EPIDEMIOLOGY AND SPECIFIC RISK FACTORS FOR MALIGNANT LYMPHOMA IN THE SINGAPORE POPULATION

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NATIONAL UNIVERSITY OF SINGAPORE

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(MMedSc), HKU

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DECLARATION

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

The data used for the analysis include:

1) The aggregated non-identifiable lymphoma incidence from 1968 to 2007 which was obtained from the Singapore Cancer Registry, with the approval from Ministry of Health for research purposes;

2) Questionnaire data from the Singapore Lymphoma Study which was approved by the Principal Investigator A/Prof Adeline Seow. The study was funded by BMRC grant from A*STAR (ref: #04/1/21/19/336) for the period of Feb 2005 to July 2010. We have obtained ethics approvals from the respective ethics committee (EC) / institutional review board (IRB) at NUS (ref: 04-045), National Health Group (NHG IRB ref: B/04/114), Singapore General Hospital (SGH IRB ref: #190/2004) and National Cancer Centre (NCC EC ref: 04-12-LYM) for conducting this study.

During my PhD candidature as a part time student, I have contributed to the following:

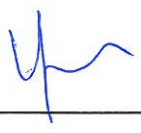
1) confirmation of lymphoma diagnosis (100% of all cases) (2005 to 2008);

2) recruitment and interview of cases and controls in ~200 participants (15% of all interviews) (2005 to 2008);

3) set up of database (100%) and data entry of ~300 questionnaires (23% of all interviews) (2008 to 2009);

4) data cleaning and data analysis (100%) (2009 to 2012)

This thesis has also not been submitted for any degree in any university previously.



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SUMMARY

Background

The incidence of lymphoid neoplasms has been rising steadily over the past decades in Singapore, and there were no apparent reasons to account for its highest lymphoma rate in Asia. The aims of this thesis are to explore the influence of temporal variations on lymphoma rates and understand the aetiology factors including occupation, sun exposure behaviours as well as smoking and drinking habits which could be related to its rise in Singapore.

Study I – Trends of lymphoma in Singapore (1968-2007)

We describe changes in lymphoma cancer incidence based on various classifications using aggregate, non-identifiable lymphoma incidence data from the Singapore Cancer Registry for the period 1968 to 2007. Age-period-cohort (APC) modelling was performed on 7,217 individuals aged 15 to 79 years with lymphoid neoplasms using Poisson regression.

Our analysis of non-Hodgkin lymphoma indicated that the full APC model provided the best fit. Apart from age, both period and cohort effects have significant impacts on the population trend. When Hodgkin lymphoma was grouped as part of lymphoid neoplasms, the period effect disappeared from the model. Our study is the first analysis on incidence trends using the updated WHO classifications of lymphoid neoplasms, and the results suggested both age and birth cohort effect contributed to the rise.

Study II to IV : Singapore Lymphoma Study (2004-2008)

In studies II to IV, a hospital-based case-control study of 541 incident cases of lymphoid neoplasms and 830 controls aged 18 years and above were recruited between 2004-2008. Participants were interviewed using structured questionnaire to elicit information on occupational history, lifestyle factors such sun exposure histories cigarette smoking and alcohol drinking. Information on basic demographics and potential confounders were also collected. The effect of various risk factors on lymphoma were quantified using odds ratios (OR) and 95% confidence intervals (CI) via the unconditional logistic regression.

Study II examines the association between occupational history and the risk of lymphoma. There was no association with any occupational groups except the teaching profession. As compared with those who were never employed in teaching profession, teachers who taught <10 years had increased NHL risk [OR 2.43, 95%CI 1.11-5.33].

Study III investigates the association between sun exposure and the risk of lymphoma. Regular leisure sun exposure on non-school days during childhood [OR 0.62, 95%CI 0.46-0.83] and non-working days in adulthood [OR 0.70, 95%CI 0.51-0.97] reduced the risk of NHL. The protective effect was more evident among females.

Study IV examines the smoking and drinking behaviours and risk of lymphoma. Compared with non-drinkers, alcohol drinkers had a lower risk of NHL overall [OR 0.68, 95%CI 0.48-0.97], regardless of beverages types. The protective effect was observed in those started drinking after 19 years old [OR 0.47,

95%CI 0.28-0.79], and in those drank at least 40 standard drinks per week [OR 0.50, 95% 0.27-0.93]. No relations between cigarette smoking and lymphoma risk among smokers were detected.

Conclusion

Age and cohort effects have contributed to the rise of lymphoid neoplasms over the years. Lifestyles such as sunlight exposure and alcohol drinking might be inversely associated with NHL risk, while teaching occupation increased its risk. Future epidemiology studies with bigger sample size are needed to extend investigations to rare subtype levels.

LIST OF MANUSCRIPTS AND POSTER PRESENTATIONS

Manuscripts

1. Chia SE, Wong Kin-Yoke, Tai BC. **Occupation and risk of non-Hodgkin lymphoma in Singapore.** *Occupational Medicine (Lond). 2012; 62(1):29-33.*

2. Wong Kin-Yoke, Tai BC, Chia SE, Kuperan P, Lee KM, Lim ST, Loong S, Mow B, Ng SB, Tan L, Tan SY, Tan SH, Tao M, Wong A, Wong GC and Seow A. **Sun exposure and risk of lymphoid neoplasms in Singapore**. *Cancer Causes Controls, 2012; 23:1055-1064.*

3. Wong Kin-Yoke, Chia SE, Seow A and Tai BC. **Trends of lymphoid neoplasms in Singapore (1968-2007): Age-period-cohort analysis**. *(manuscript pending review)*

4. Wong Kin-Yoke, Chia SE, Kuperan P, Lee KM, Lim ST, Loong S, Mow B, Ng SB, Tan L, Tan SY, Tan SH, Tao M, Wong A, Wong GC and Seow A. **Cigarette smoking, alcohol drinking and and the risk of lymphoid neoplasms in Singapore.** *(manuscript pending review)*

Poster presentation at international conference

1. Kin-Yoke Wong, S-E Chia, P Kuperan, K-M Lee, S Loong, B Mow, S-B Ng, L Tan, S-H Tan, M Tao, G-C Wong and A Seow. Malignant lymphomas in an Asian population: characteristics of cases and distribution of histological subtypes in the Singapore lymphoma study [abstract]. In: American Association for Cancer Research Annual Meeting: Proceedings; 2007 Apr 14-18; Los Angeles, CA. Philadelphia (PA): AACR; 2007. Abstract number 63.

2. Kin-Yoke Wong, S-E Chia, P Kuperan, K-M Lee, S-T Lim, S Loong, B Mow, S-B Ng, L Tan, S-Y Tan, S-H Tan, M Tao, G-C Wong and A Seow. Sun exposure and the risk of malignant lymphoma in an Asian population: The Singapore lymphoma study. [abstract]. In: Proceedings of the 101st Annual Meeting of the American Association for Cancer Research; 2010 Apr 17-21; Washington, DC. Philadelphia (PA): AACR; 2010. Abstract number 1824.

3. Kin-Yoke Wong, S-E Chia. Occupation and the risk of malignant lymphoma in an Asian population: The Singapore Lymphoma Study. In: Proceedings of the 2nd Asian Conference on Environmental Mutagens (ACEM); 2010 Dec 15-18; Pattaya, Thailand. Abstract number P4-01.

LIST OF ABBREVIATIONS

1,25(OH)D	1,25-dihydroxyvitamin D
25(OH)D	25-hyrdoxyvitamin D
95% CI	95% confidence interval
AIDS	Acquired immune deficiency syndrome
APC	Age-period-cohort
ASR	Age-standardized rate
BMI	Body mass index
BL	Burkitt lymphoma
CLL/SLL	Chronic Lymphocytic Leukaemia / Small Lymphocytic Lymphoma
CT	Computer tomography
DLBCL	Diffuse large B-cell lymphoma
DM	Diabetes Mellitus
EBV	*Epstein-barr* virus
EC	Ethnics committee
ECOG	Eastern Cooperative Oncology Group
EPIC	European prospective investigation into cancer and nutrition
EpiLymph	Environmental exposures and lymphoid neoplasms
FISH	Fluorescence *in situ* hybridization
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GWAS	Genome-wide association study
HBV / HCV	Hepatitis B virus / Hepatitis C virus
HD / HL	Hodgkin's disease / Hodgkin lymphoma
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
HPV8	Human herpesvirus 8
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
InterLymph	International Lymphoma Epidemiology Consortium
ILSG	International Lymphoma Study Group
IPI	International Prognostic Index
IRB	institutional review board

LD	Lymphocyte depletion
LDH	Lactate dehydrogenase
LN	Lymphoid neoplasms
LP	Lymphocyte predominant
MC	Mixed cellularity
MCL	Mantel cell lymphoma
MF/SS	Mycosis Fungoides / Sézary syndrome
MET	Metabolic Equivalent (ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ) $kg^{-1}h^{-1}$) (Ainsworth *et al.* 2000)
MM	Multiple myeloma
MRI	Magnetic resonance imaging
NHL	non-Hodgkin lymphoma
NK	Natural killer
NSHL	Nodular sclerosis
OR	Odds ratio
PCM	Plasma cell myeloma
PET	Positron emission tomography
PTCL	Peripheral T-cell lymphoma
py	person-years
REAL	Revised European American Lymphoma
Ref	Reference
RR	Relative risk
SES	Social economic status
SCALE study	Scandinavian lymphoma etiology study
SEER	Registry
SIR	Standardized incidence ratio
SLE	Systemic Lupus Erythematosus
SLS	Singapore Lymphoma Study
SNP	Single-neocleotide polymorphism
UK	United Kingdom
US	United States
UV	Ultraviolet
WHO	World Health Organization

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Chapter 1

Background of lymphoid malignancies

Lymphoid neoplasms (LN), which generally called lymphoma, are heterogeneous groups of malignancies in the immune system. The major neoplastic groupings of the lymphoid neoplasms are known as **Hodgkin lymphoma (HL)** and **non-Hodgkin lymphoma (NHL)**. Both malignancies occur in B- or T-lymphocytes which normally protects us from infection and disease. Different lymphomas have various origins, and they derived at various stage of cell differentiation. Precursor B-lymphocytes arise from bone marrow, and differentiate into mature lymphocytes at lymph nodes (across marginal zone, mantle zone, and germinal centre), and recirculate around the body. Similarly the precursor T-lymphocytes bypass to thymus, before it enters lymph nodes or other extra-nodal tissue. Majority of lymphomas are B-cell lymphomas.

Since lymphocytes travel along the lymphatic system, most lymphomas have nodal involvement, i.e. lymphoma found in lymph nodes such as cervical, infraclavicular, occipital, axillary, mediastinum, retroperitoneal, hilar, mesenteric, para-aortic, iliac, inguinal, or even epitrochlear and brachial or popliteal lymph nodes. Locations including Waldeyer ring, tonsil, thymus, spleen, or bone marrow are also common in lymphoma. Other common sites found outside of lymphatic systems, i.e. extra-nodal involvement, including central nervous system, stomach, lung, small intestine, or skin. It is therefore lymphoma presented in both solid phase as solid tumour in extra-nodal organs, and leukemic phase in bone marrow and circulating blood.

1.1 Signs and symptoms

Some types of lymphoma are slow-growing, i.e. **indolent**, or **low-grade** lymphomas, it is usually asymptomatic unless it caused compression at organs, and treatments may not be needed urgently. Others are fast-growing and causing rapid deterioration, i.e. **aggressive**, or **high-grade** lymphomas. Treatments are needed as soon as possible after diagnosis, most are respond well to treatment and hence curable. Once there are signs and symptoms, it is important to have physical examination by medical doctors to rule out the possibility, since some of the symptoms are common between infections, autoimmune diseases and lymphoma. Depends on the aggressiveness of lymphoma, symptoms may last from weeks to months, or even years (Emmanouilides & Casciato 2004; UK).

Local symptoms are generally related to the disease of presentation, including 1) enlarged but usually painless lymph nodes (i.e. lymphadenopathy) in the neck, armpits or groin area; 2) chest symptoms - coughing, breathlessness or chest pain; 3) abdominal symptoms – pain or discomfort may be due to organomegaly, any swellings, indigestion, change in bowel habit e.g. diarrhoea; 4) pain or ache in bones may reflect localized area of bone destruction; 5) back pain due to massive retroperitoneal nodal involvement; 6) brain and nerve symptoms: dizziness, numbness, tingling, weakness in limb, visual problem, memory problems; 7) skin problem – lumps, redness or itchy patches; or 8) lumps in other unusual places e.g. in the breast, testicle, nose, jaw etc.

Other symptoms are affecting overall, i.e. systematic symptoms, including unexplained weight loss >10% in the past 6 months, fever >38^{o}C, drenching night sweats, extreme tiredness and itch, or difficulty fighting off infections.

1.2 Diagnosis and staging

To order to confirm involvement of lymphoma, a biopsy (fine needle biopsy or excision biopsy) at the site of presentation is needed. Lymphomas are distinguished by the cell of origin and morphology, immunologic phenotyping, location of tumour, and genetic approach such as polymerase chain reaction. Other clinical evaluation are including physical examination, blood test e.g. lactate dehydrogenase (LDH) and human immunodeficiency virus (HIV), bone marrow biopsy, imaging techniques e.g. x-ray, computer topography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET).

The extent to where the cancer has spread in the body is called the **stage** of disease. The performance status of patients is measured by ECOG score (**Table 1.1**), a score introduced by the Eastern Cooperative Oncology Group, which indicate how well a patient is function at the time of presentation. This is one of the predictive variables for prognosis of lymphoma.

Table 1.1 ECOG score

Grade	ECOG
0	• Fully active, able to carry on all pre-disease performance without restriction.
1	• Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	• Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	• Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	• Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	• Dead.

The tumour stage of patients is usually determined by the Ann Arbor staging system (Lister *et al.* 1989), which was originally developed for Hodgkin's disease (**Table 1.2**). Under the system, there are designations applicable to any disease stage based on the symptoms presented, called A, B, E, and X. High fever, night sweats, weight loss are called "B symptoms", which is associated with poor prognosis. For example, if a stage 2 patient presented with the above symptoms, it will be called "Stage 2B", or else will be called "Stage 2A". "E" stands for single isolated site of extra-nodal disease or extra-nodal extension, i.e. lymphoma has spread to organ or area outside lymphatic system. "X" refers bulky disease, a mediastinal mass exceeding 1/3 the maximum transverse thoracic diameter, or the presence of nodal mass greater than 10cm.

Table 1.2 Cotswolds Modification of Ann Arbor Staging system (Lister *et al.* 1989)

Stage	Area of involvement
I (early)	• Single lymph node group
II (early)	• Multiple lymph node groups and/or an organ on the same side of diaphragm
III (advanced)	• Multiple lymph node groups and/or an organ on both sides of diaphragm and/or an organ or other area both above and below the diaphragm
IV (advanced)	• Multiple extra-nodal sites or lymph node and extra-nodal disease e.g. bone marrow, lungs, liver and skin

Since the patterns of disease spread in HL and NHL are different, the Ann Arbor classification is not very sensitive to predict prognosis of patients with aggressive NHL. A new system incorporated with clinical features called International Prognostic Index (IPI) was developed (1993) to identify 4 risk groups based on the treatment response rates of other aggressive NHLs (**Table 1.3**).

Table 1.3 International Prognostic Index (IPI) (1993)

Prognostic factors for all patients	IPI	
• Age >60 years	• Low	0 or 1
• Serum LDH >1xnormal	• Low intermediate	2
• Performance status 2-4		3
• Stage III-IV	• High intermediate	4 or 5
• Extra-nodal involvement >1 site	• High	

1.3 Classification of lymphoid neoplasms

Hodgkin's disease or Hodgkin lymphoma: In 1832, a rare disease was first described by Thomas Hodgkin (1798-1866) as "some morbid appearance of the absorbent glands and spleen". The disease was named **Hodgkin's disease (HD)** in 1865. The Rye Classification for Hodgkin Disease was developed by Lukes and Butler, modified and presented at the conference in Rye, New York in 1966. There were 4 subtypes called lymphocyte predominant (LP), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte depletion (LD), with decreasing prognosis from most favourable to least favourable respectively. The abnormal B-lymphocyte called Reed-Sternberg cell, which derived from B-cell germinal centre, is particularly found in this type of lymphoma. This cell is the standard diagnosis of Hodgkin disease (NCI). This classification has been used for another 30 years, before an additional subtype lymphocyte-rich classical Hodgkin lymphoma (LR) was proposed in Revised European-American Lymphoma (REAL) classification in 1994, and renamed as **Hodgkin Lymphoma** in 2001. HL accounts for about 10% of all lymphoid neoplasms, all other types of lymphomas are called non-Hodgkin's lymphoma (Melbye *et al.* 2008).

Non-Hodgkin lymphoma – The classification of NHL has been evolving in the past few decades in Europe and the United States. A new classification was launched in almost every decade. **Table 1.4** summarizes the early classifications of lymphoid neoplasms. The Rappaport system, which was based only on the morphology of cell differentiation, was one of the earliest systems used until mid-70s. In Europe, Karl Lennert developed the Kiel system in 1974, which was based on cellular morphology and immunologic characteristics of T- and B-lymphocytes; while similar systems called the Lukes

and Collins Classification were used in the United States. In 1982, the Working Formulation was introduced by the National Cancer Institute. The classification was further modified based on cell differentiation, cell size, and whether or not the cell was cleaved. This led to the distinction between low-grade and high-grade cancers.

In 1994, the International Lymphoma Study Group (ILSG) proposed that lymphomas should be grouped as clinical-pathologic entities based on morphologic, immunologic and genetic characteristics according to cell origin. This led to the development of the REAL classification, which was further revised in 2001 and became the new international standard for NHL worldwide today. The World Health Organization (WHO) classification was based on cell appearance, growth pattern of cancerous cells and genetic features. **Table 1.5** summarizes the entities of WHO classification, and the equivalents in the updated Kiel and REAL classification systems (Chan 2001; Gallus *et al.* 2004; Jaffe *et al.* 2001; Network). The latest updated version was released in 2008 (Campo *et al.* 2011; Jaffe 2009) and presented in **Table 1.6**.

Table 1.4 Early classifications of NHL a) The Rappaport classification, b) Working Formulation.

a) The Rappaport classification (1960s)

Description
• Well-differentiated cells, or small lymphocytic lymphoma • Poorly differentiated cells, or follicular centre cell lymphoma with a large component of small-cleaved cells • Histocytic cells, or large cell lymphoma

b) Working Formulation (1982)

Description	
Low grade	A. Small lymphocytic; plasmacytoid B. Follicular, small cleaved cell C. Follicular, mixed (small cleaved and large cell)
Intermediate grade	D. Follicular, large cell E. Diffuse, small cleaved cell F. Diffuse, mixed (small cleaved and large cell) G. Diffuse, large cell
High grade	H. Immunoblastic (large cell) I. Lymphoblastic J. Small, noncleaved (Burkitt, non-Burkitt)

Table 1.5 Entities of the WHO classification for lymphoid neoplasms and their equivalents in the updated Kiel classification and the REAL classification. (NCI)

Kiel (1974)	REAL (1994)	WHO (2001)	ICD-O 3rd Ed
	HODGKIN'S DISEASE	**HODGKIN LYMPHOMA**	
Not listed in the Kiel classification	Lymphocyte predominance (Paragranuloma)	Nodular lymphocyte predominant Hodgkin lymphoma	9659/3
	Classical Hodgkin's disease	Classical Hodgkin lymphoma	9650/3
	• Nodular sclerosis	• Nodular sclerosis	9663/3
	• *Lymphocyte-rich classical HD*	• Lymphocyte-rich	9651/3
	• Mixed cellularity	• Mixed cellularity	9652/3
	• Lymphocyte depletion	• Lymphocyte-depleted	9653/3
B-CELL LYMPHOMAS	**B-CELL NEOPLASMS**	**B-CELL NEOPLASMS**	
	Precursor B-cell neoplasm	**Precursor B-cell neoplasm**	
Acute lymphoblastic B-cell leukaemia	Precursor B lymphoblastic leukaemia/ lymphoma	Precursor B lymphoblastic leukaemia/ lymphoma	9835/3
B lymphoblastic lymphoma			9728/3
	Peripheral B-cell neoplasms	**Mature B-cell neoplasms**	
B-cell chronic lymphocytic leukaemia	B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma/	Chronic lymphocytic leukaemia/small lymphocytic lymphomas	9823/3
Immunocytoma, lymphoplasmacytoid type			9670/3
B-cell prolymphocytic leukaemia	B-cell prolymphocytic leukaemia	B-cell prolymphocytic leukaemia	9833/3
Immunocytoma, lymphoplasmacytic type	Lymphoplasmacytoid lymphoma/ immunocytoma	Lymphoplasmacytic lymphoma	9671/3
	Splenic marginal zone lymphoma (±villous lymphocytes)	Splenic marginal zone lymphoma (±villous lymphocytes)	9689/3
Hairy cell leukaemia	Hairy cell leukaemia	Hairy cell leukaemia	9940/3
Plasmacytic lymphoma (Plasmacytoma)	Plasmacytoma / Plasma cell myeloma	Plasma cell neoplasms	
		• Plasma cell myeloma	9732/3
		• Solitary plasmacytoma of bone	9731/3
		• Extraosseous plasmacytoma	9734/3
		Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Monocytoid B-cell lymphoma	*Marginal zone B-cell lymphoma, nodal (±monocytoid B cells)*	Nodal marginal zone B-cell lymphoma (±monocytoid cells)	9699/3

Table 1.5 (cont.)

Kiel (1974)	REAL (1994)	WHO (2001)	ICD-O 3rd Ed
	Peripheral B-cell neoplasms	**Mature B-cell neoplasms**	
Centroblastic-centrocytic lymphoma, Follicular, follicular and diffuse - with an increased no of centroblasts	Follicle centre lymphoma, follicular • *Grade I* • *Grade II* • *Grade III*	Follicular lymphoma • Grade 1 • Grade 2 • Grade 3a • Grade 3b	9690/3
Centroblastic lymphoma, follicular			
Centroblastic-centrocytic lymphoma, diffuse	*Follicle centre lymphoma, diffuse, small cell*	Diffuse follicle centre lymphoma	
Centrocytic (mantle cell) lymphoma Centroblastic lymphoma, centrocytoid	Mantle cell lymphoma	Mantle cell lymphoma	9673/3
Centroblastic lymphoma, diffuse	Diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma (variants) • centroblastic • immunoblastic • anaplastic • T-cell/histiocyte rich • plasmablastic • with expression of full length ALK (IgA+)	9680/3
B immunoblastic lymphoma			
B-cell large anaplastic lymphoma			
	DLBCL subtype: Primary mediastinal (thymic) large B-cell lymphoma	Mediastinal (thymic) large B-cell lymphoma	9679/3
Angio-endotheliotropic (intravascular) lymphoma	Diffuse large B-cell lymphoma	Intravascular large B-cell lymphoma	9680/3
	Diffuse large B-cell lymphoma	Primary effusion lymphoma	9678/3
Burkitt lymphoma (BL) • BL with intracytoplasmic immunoglobulin	Burkitt's lymphoma *DLBCL subtype: High-grade B-cell lymphoma, Burkitt-like*	Burkitt lymphoma (BL) BL with plasmacytoid differentiation atyptical BL / Burkitt-like	9687/3
	Burkitt leukaemia	• Burkitt leukaemia	9826/3
		B-cell proliferations of uncertain malignant potential	
Lymphomatoid granulomatosis (Liebow)		Lymphomatoid granulomatosis	9766/1
		Post-transplant lymphoproliferative disorder, Polymorphic	9970/1

Table 1.5 (cont.)

Kiel (1974)	REAL (1994)	WHO (2001)	ICD-O 3rd Ed
T-CELL LYMPHOMAS	**T-CELL AND PUTATIVE NK-CELL NEOPLASMS**	**T-CELL AND NK-CELL NEOPLASMS**	
	Precursor T-cell neoplasm	**Precursor T-cell neoplasm**	
Acute lymphoblastic T-cell leukaemia T lymphoblastic lymphoma	Precursor T lymphoblastic leukaemia / lymphoma	Precursor T lymphoblastic leukaemia / lymphoma	9837/3 9729/3
		Blastic NK-cell lymphoma	9727/3
	Peripheral T-cell and NK-cell neoplasms	**Mature T-cell and NK-cell neoplasms**	
T-cell prolymphocytic leukaemia/ T-cell chronic lymphocytic leukaemia (knobby-type)	T-cell prolymphocytic leukaemia/ T-cell chronic lymphocytic leukaemia	T-cell prolymphocytic leukaemia	9834/3
T-cell chronic lymphocytic leukaemia (azurophilic-type)	Large granular lymphocyte leukaemia (LGL) of T-cell type	T-cell large granular lymphocytic leukaemia	9831/3
	Large granular lymphocyte leukaemia (LGL) of T-cell type	Aggressive NK-cell leukaemia	9948/3
T-cell lymphoma, small cell type, pleomorphic medium and large cell type (HTLV-1+)	Adult T-cell lymphoma/ leukaemia (HTLV-1+) Angiocentric T-cell lymphoma Intestinal T-cell lymphoma (±enteropathy) *Hepatosplenic $\gamma\delta$ T-cell lymphoma* *Subcutaneous panniculitis T-cell lymphoma*	Adult T-cell leukaemia/lymphoma Extranodal NK-/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Hepatosplenic T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma	9827/3 9719/3 9717/3 9716/3 9708/3
Small cell cerebriform (mycosis fungoides/ Sezary syndrome)	Mycosis fungoides Sezary syndrome Primary cutaneous anaplastic large cell (CD30+) lymphoma	Mycosis fungoides Sezary syndrome Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	9700/3 9701/3 9718/3
Pleomorphic small, medium-sized and large T-cell lymphoma T-zone lymphoma Lymphoepithelioid (Lennert's) lymphoma	Peripheral T-cell lymphoma, unspecified	Peripheral T-cell lymphoma, unspecified • T-zone variant • Lymphoepithelioid cell variant (Lennert lymphoma)	9702/3
Angioimmunoblastic (AILD, LgX-type)	Angioimmunoblastic T-cell lymphoma	Angioimmunoblastic T-cell lymphoma	9705/3
T-cell large anaplastic (Ki-1+) lymphoma	Anaplastic large cell lymphoma, CD30+ (T-/null-cell types)	Anaplastic large cell lymphoma	9714/3
		T-cell proliferation of uncertain malignant potential	
		Lymphomatoid papulosis	9718/1

Table 1.6 WHO classification of tumors of hematopoietic and lymphoid tissues (updated in 2008) (Swerdlow *et al.* 2008)

Mature B-cell neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable**
  - *Splenic diffuse red pulp small B-cell lymphoma**
  - *Hairy cell leukemia variant**
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma**
- Follicular lymphoma
  - *Pediatric follicular lymphoma**
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - T-cell/histiocyte rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - *EBV-positive DLBCL of the elderly**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T-cell and NK-cell neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK-cells**
- Aggressive NK-cell leukemia
- Systemic EBV-positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma**
- *Primary cutaneous CD4+ small/medium T-cell lymphoma**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- *Anaplastic large cell lymphoma, ALK-negative**

Hodgkin lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma

Posttransplantation lymphoproliferative disorders (PTLDs)

- Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)†
- Classical Hodgkin lymphoma type PTLD†

* These histologic types are provisional entities for which the WHO Working Group felt there was insufficient evidence to recognise as distinct diseases at this time.
† These lesions are classified according to the leukemia or lymphoma to which they correspond.

The features of more common lymphoid neoplasms are summarised in the followings (Aster 2003; Campo *et al.* 2011) :

a) Low grade B-cell lymphomas

- *Follicular lymphoma (FL)* is one of the most common indolent lymphoma in the world. It constitutes ~40% of adult lymphomas. These tumours express B-cell markers (CD10, CD19, and CD20) and BCL2 protein. FL is determined by Follicular Lymphoma International Prognostic Index (FLIPI) (Solal-Celigny *et al.* 2004). It is generalized lymphadenopathy and occurs in older age. Due to its slow growing nature, it does not respond to chemotherapy very well, treatments may be delayed for years, and replaced by 'watch and wait' management if patients are clinically stable with no symptoms (LFA 2011).

- *Chronic lymphocytic leukaemia/Small lymphocytic lymphoma (CLL/SLL)* is a lymphoid leukaemia expressed as both lymphoma (3-4%) and leukaemia (30%). It expresses both pan-B-cell makers (CD19, CD20 CD23) and T-cell-associated antigen (CD5). CLL is staged by Rai classification, and uncommon in Asians. It behaves similar to FL but usually involves bone marrow. (Foon & Casciato 2004; Rai *et al.* 1975).

- *Plasma cell myeloma (PCM) / Multiple myeloma (MM)* are formed by clonal expansion of a single homogenous immunoglobulin, often referred as M component. They occur mainly in middle-aged to elderly persons, with bone marrow and skeletal destruction. PCM is usually asymptomatic and does not require immediate treatment, unless organ damage is present.

b) Intermediate and high grade B-cell lymphomas:

- *Diffuse large B-cell lymphoma (DLBCL)* is the most common NHL (<50%). These are the mature B-cell tumours that express pan-B-cell antigens (CD19, CD20, and CD79a). It is an aggressive tumour with higher frequency of spreading to extra-nodal, visceral and bone marrow. Prognosis is poor but up to 50% are curable.

- *Mantel cell lymphoma (MCL)* is predominantly in older males, disseminated disease in nodes, spleen, and bone marrow. It is an aggressive and difficult to cure tumour. Similar to CLL/SLL, the tumour cells expressed pan-B-cell antigens, and surface IgM and IgD, and high level of cyclin D1 protein.

- *Burkitt lymphoma (BL)* is endemic in Africa but sporadic in other countries. BL expresses surface IgM and pan-B-markers (CD19) and CD10 antigen. It is well-known its relation with immunosuppression (e.g. HIV/AIDS). Extranodal visceral involvement but responsive to therapy.

c) T/NK-cell lymphomas

- *Mycosis Fungoides (MF) / Sézary syndrome (SS)* is the most common type of cutaneous lymphoma, with expression of CD4 T-cells. It is very indolent and presents with local or generalized skin involvement.

- *Peripheral T-cell lymphoma (PTCL)* is a common T-cell lymphoma (CD3+) in adults, generally with poor prognosis.

d) Hodgkin lymphoma

- *HL, nodular sclerosis (HL NS)* is the most common form of HL. Usually pan-B-cell markers and T-cell markers are not expressed, and it is identified by Reed-Sternberg cell. It affects mostly in young women, and presented with cervical or mediastinal lymphadenopathy.

- *HL, mixed cellularity (HL MC)* is the second most common HL. It is identified by the classic Reed-Sternberg cell, CD15 and CD30 positive, in a mixed inflammatory background. Most common in men, presented with advances stage disease, and 70% of cases EBV positive.

1.4 Changes in incidence of lymphoid neoplasms

The GLOBOCAN project used the most recent cancer data available from the International Agency for Research on Cancer (IARC) to provide the estimates of the incidence and mortality of major types of cancers for 184 countries in the world (Ferlay *et al.* 2010). According to the GLOBOCAN estimation in 2008, of the 12.6 million new cancer cases (52.4% males, 47.6% females), 2.8% were non-Hodgkin lymphoma (3.0% males, 2.6% females), 0.8% multiple myeloma (0.8% males, 0.8% females), and 0.5% Hodgkin lymphoma (0.6% males, 0.5% females). Since we cannot separate the acute lymphoblastic lymphoma (i.e. a subtype of lymphoid neoplasms under WHO classification, previously grouped as leukaemia) from acute myeloid leukaemia under the “Leukaemia” category, therefore they were not included in the followings.

a) Variation in incidence across countries and gender

Lymphoid neoplasms, in terms of HL, NHL and MM subtypes, vary across countries. Across all racial and ethnic groups in these countries, cultural and genetic factors may play a role in the cancer incidence. The age standardized rate (ASR) of incidence and mortality of LN is universally higher in men than women. The estimated age-standardized (world) rates of NHL, HL and PCM by gender were presented in **Figure 1.1**.

Non-Hodgkin lymphoma: When the world is divided into 6 major regions, the ASR per 100,000 person-years (py) of NHL in 2008 was the highest in North America (16.2 per 100,000 py in males, 11.5 per 100,000 py in females), followed by the Oceania (i.e. Australia/New Zealand) (13.6 per 100,000 py in males, 9.6 per 100,000 py in females), and Europe (8.5 per 100,000 py in males, 5.8 per 100,000 py in females). The lowest ASR was in Asia (3.9 per 100,000 py in males, 2.6 per 100,000 py in females), despite the number of incidence being the largest (n=75,866 in males and n=52,233 in females). Considering at country level, the ASR of NHL was the highest in Israel (18.5 per 100,000 py in males, 14.9 per 100,000 py in females); followed by the United States of America. The estimates in Singapore (9.6 per 100,000 py in males and 5.9 per 100,000 py in females) were higher than most of the European countries (Ferlay *et al.* 2010).

Hodgkin lymphoma: The pattern of HL was similar to NHL, where higher rates were reported in the Western countries. The highest and lowest ASR of HL was in North America (2.6 per 100,000 py in males, 2.2 per 100,000 py in females), and Asia (0.8 per 100,000 py in males, 0.5 per 100,000 py in females)

respectively. When comparing at country levels, Israel, Cyprus and Lebanon are the countries with highest ASR of HL (Ferlay *et al.* 2010).

Multiple myeloma: The incidence of MM is the most prevalent in Europe, but the ASR is still the highest in North America (4.8 per 100,000 py in males and 3.0 per 100,000 py in females), and the lowest in Asia (0.8 per 100,000 py in males and 0.6 per 100,000 py in females). France and Luxembourg are the countries with the highest ASR of MM in males and females respectively (Ferlay *et al.* 2010).

b) Variation in incidence across age

HL, NHL and PCM have very different incidence pattern in terms of age at diagnosis (**Figure 1.2)**. HL is bimodal, the incidence is low in childhood but increases during adolescence to peak in young adulthood (i.e. first peak), the rate decrease gradually and then increases steadily again from 40 years old onwards (i.e. second peak). As for NHL, the rate increased exponentially with age from adolescence, and MM commonly occurred after age 40 years and its rate increased with age.

Figure 1.1 Estimated ASR of incidence per 100,000 person years of NHL, HL and MM across the world by gender. Source: GLOBOCAN 2008 (Ferlay *et al.* 2010)

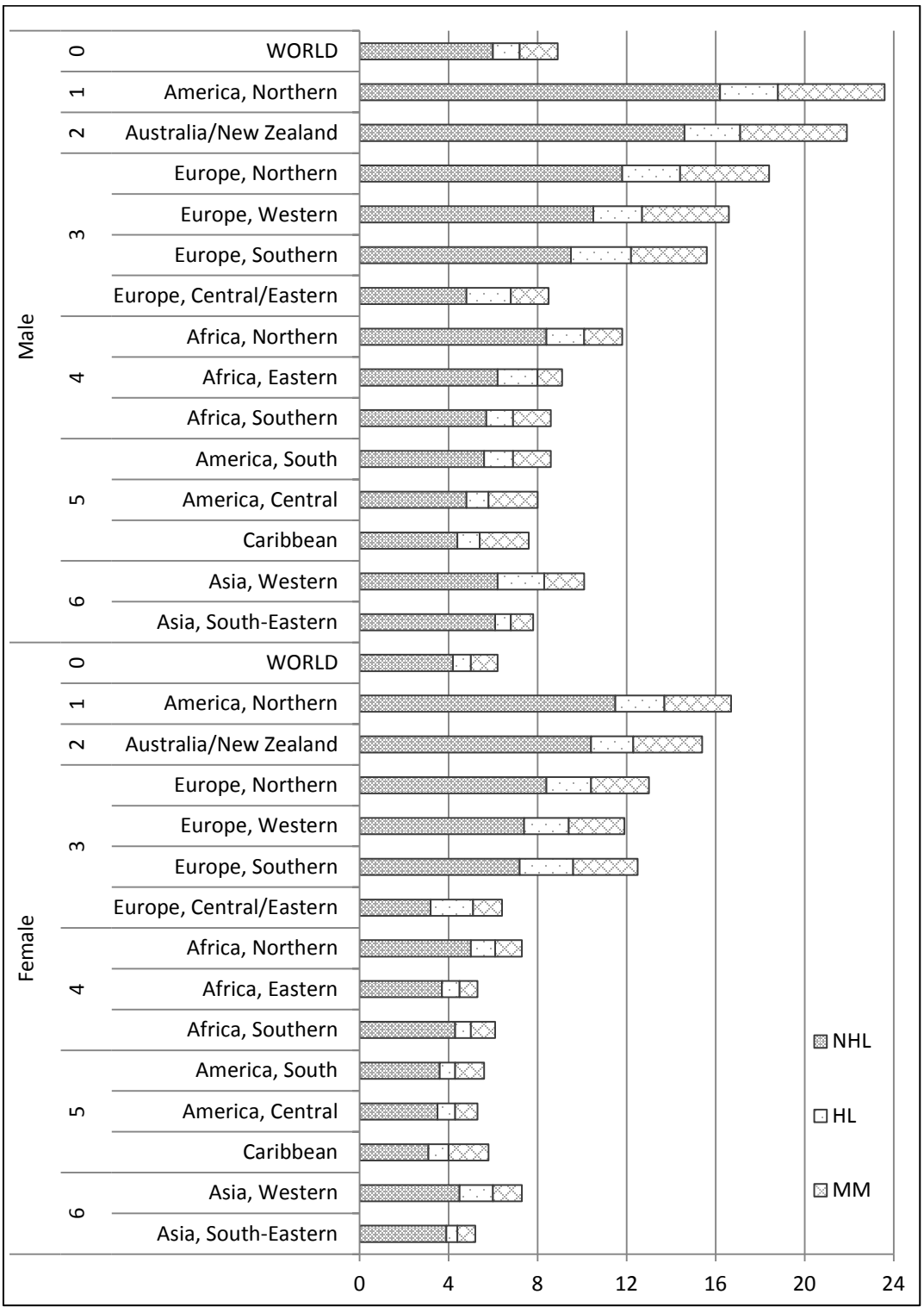
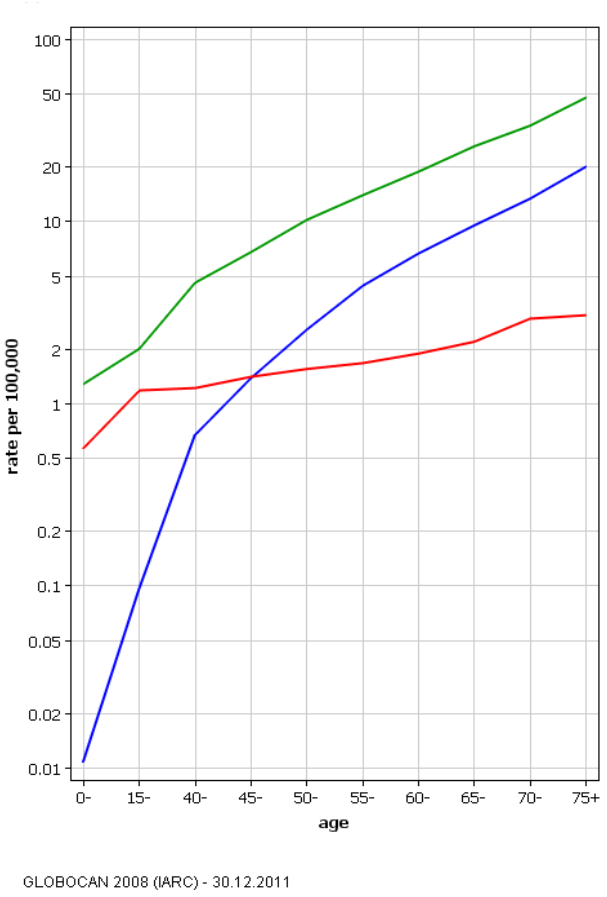
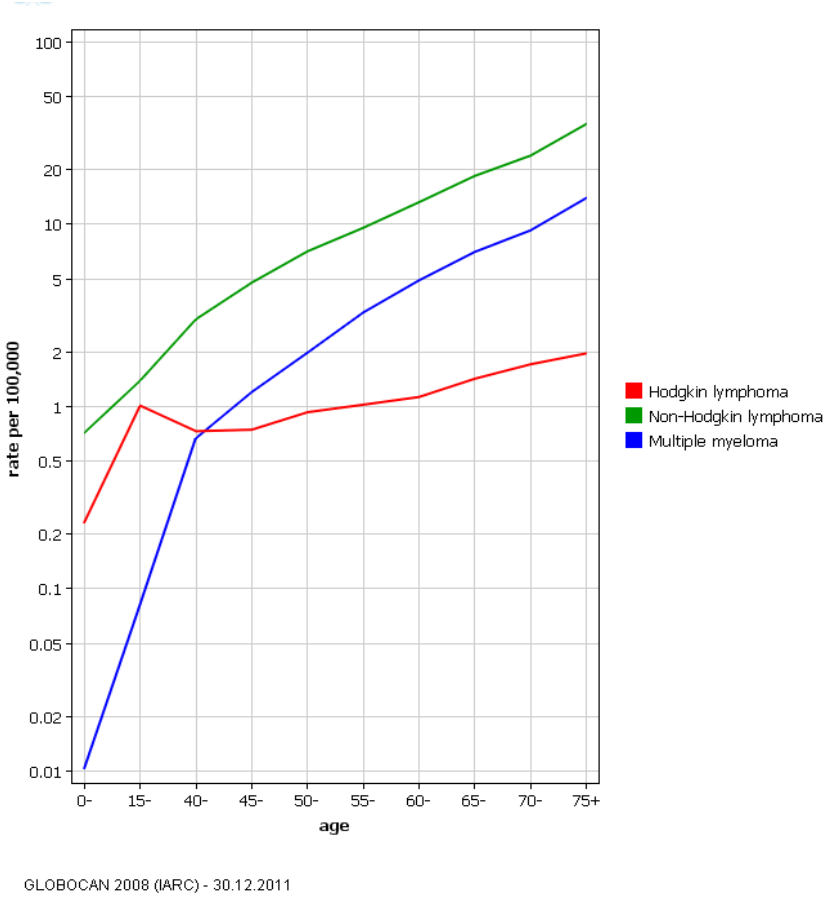


Figure 1.2 Estimated age standardized incidence rate of NHL, HL and MM in the world according to age at diagnosis and gender. Source: GLOBOCAN 2008 (Ferlay *et al.* 2010).

(a) male



(b) female



c) Changes in lymphoma trends over the years

Non-Hodgkin lymphoma: Many studies reported that the incidence of NHL has risen dramatically in the past few decades. Majority of the reports from the West, including US Connecticut (1935-1991) (Polednak 1994), SEER (1973-1995) (Varterasian *et al.* 2000), Canada (1970-1996) (Liu *et al.* 2003), Denmark (1943-1989) (Hjalgrim *et al.* 1996), Italy (1974-1993) (Broccia *et al.* 2001), Spain (1973-1991) (Pollan *et al.* 1998), UK (1984-1993) (McNally *et al.* 1999), and 7 countries across Europe (1985-1992) (Cartwright *et al.* 1999) suggested at least 3% increase per year in NHL incident rates. The rate of increase started to level off in early 1990s in Sweden/Denmark (1960-2003) (Sandin *et al.* 2006), Austria (1991-2000) (Mitterlechner *et al.* 2006) and Kuwait (1998-2006) (Ameen *et al.* 2010). Decreasing NHL trend was observed in Tunisia (1993-2006) (Missaoui *et al.* 2010) and Egypt (1995-2004) (Abdel-Fattah & Yassine 2007), although increasing trend was still observed in Pakistan between 1995-2002 (Bhurgri *et al.* 2005).

Hodgkin lymphoma : Adamson *et al* (2007) reported the time trends of HL in 13 European countries from 1953 to 2000, and found the incidence increased up to 1970s and tended to decline afterwards (Adamson *et al.* 2007). The observed downward trend was supported by the analysis of IARC cancer registries (1973-1997) (Katanoda & Yako-Suketomo 2008), and a UK study between 1984-1993 which reported a 2.4% annual decrease (McNally *et al.* 1999). Decreased incidence of HL was observed for those above 40 years old, but a significant increase among adolescents and young adults was reported in Israel (Ariad *et al.* 2009), Connecticut (Chen *et al.* 1997), Nordic countries (Hjalgrim *et al.* 2001) and Singapore (Hjalgrim *et al.* 2008).

d) Trends of lymphoid neoplasms in Singapore

The Singapore Cancer Registry has been collecting and reporting cancer statistics in Singapore every 5 years since 1968. In the first few reports, the age-standardized rate of lymphomas were reported separately for:

- *Non-Hodgkin lymphoma* (ICD-9: 200, 202/ICD-O-2: C00-C80 with M9590-9595, M9670-9723 and M9740-9741),
- *Hodgkin lymphoma* (ICD-9: 201/ICD-O-2: C00-C80 with M9650-9667),
- *Plasma cell tumours and immunoproliferative neoplasm* (ICD-9:203 / ICD-O-2:C42 with M9731-9732 and M9760-9768) and
- *Lymphoid leukaemia* (ICD-0: 204 / ICD-O-2: C42).

Since 2003-2007, the term ***Lymphoid neoplasms*** was used instead, and this included *non-Hodgkin lymphomas* (precursor lymphoid neoplasms, mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, immunodeficiency associated lymphoproliferative disorders, and histocytic and dendritic cell neoplasms) and *Hodgkin lymphoma* based on the WHO classification.

Table 1.7 shows lymphoid neoplasms was the 6th most common cancer in males, and 7th in females in 2003-2007, consisting of 1,309 cases (ASR 14.4 per 100,000) in males and 973 cases (ASR 10.0 per 100,000) in females respectively (M:F=1:1.3). As compared to Chinese, Malays had a higher risk of developing lymphoid neoplasm (RR 1.13 in males and 1.44 in females), and Indians the lowest risk (RR 0.75 in males and RR 0.87 in females).

Table 1.7 Incidence of lymphoid neoplasms, 2003-2007. Source: Singapore Cancer Registry Report (NRDO 2010)

	Rank	No of incidence	% of all cancers	Crude rate [b]	ASR [c]	RR (95%CI) [d]
Male						
• All[a]	6	1309	6.0	15.2	14.4	
• Chinese	7	1029	5.5	15.8	14.5	1.0
• Malay	3	178	10.2	14.8	16.9	1.13 (0.96-1.32)
• Indian	4	80	8.3	10.7	11.4	0.75 (0.60-0.94)
Female						
• All[a]	7	973	4.2	11.1	10.0	
• Chinese	9	747	3.8	11.2	9.6	1.0
• Malay	4	156	7.2	13.0	13.6	1.44 (1.21-1.71)
• Indian	5	54	5.5	7.6	8.5	0.87 (0.66-1.14)

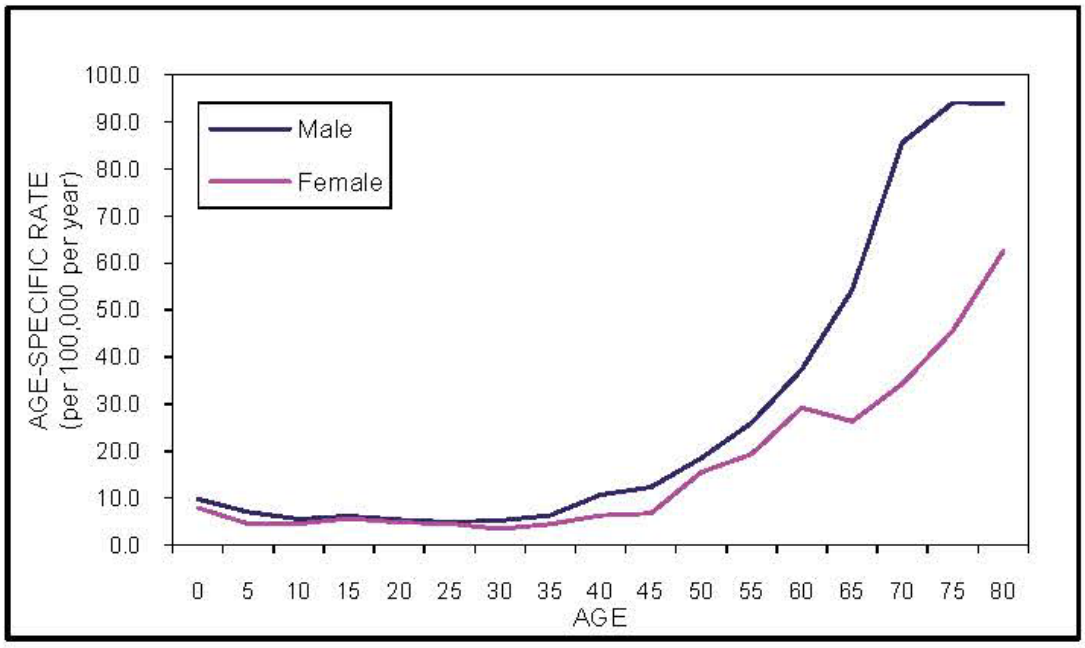
[a] All ethnicity included Chinese, Malay, Indian and others.

[b] Crude rate per 100,000 per year

[c] ASR: Age-standardized rate (per 100,000 per year) to World population.

[d] RR: Relative risk, adjusted for age and ethnic group using generalized linear regression model for binary data with the Chinese as the reference population.

Figure 1.3 Age-specific incidence of lymphoid neoplasms in Singapore, 2003-2007. Source: Singapore Cancer Registry Report (NRDO 2010).



Comparatively, the risk of lymphoid neoplasms increased slightly in early childhood and adolescence, and declined in young adults before increasing steadily from age 40 years onwards. The risk of lymphoma was consistently higher in males as compared with females across all age groups (**Figure 1.3**).

According to the Singapore Cancer Registry report 2003-2007, the average annual change in lymphoid neoplasms was 2.4% in males and 4.0% in females respectively during the period 1998 to 2007 (**Table 1.8**). Lymphoid neoplasms was ranked the third highest in children under 15 years old, comprising 14.9% and 11.1% for males and females respectively of all cancers recorded in this age group. A striking increase of 9.7% per year was noted in young females, which could not be accounted for.

While most of the HL increases around the world was noted in adolescence and young adults, previous study on HL in Singapore showed the peak increase at age 15-19 and 20-24 years (Hjalgrim *et al.* 2008), which may account for the rise in the 15-34 age groups.

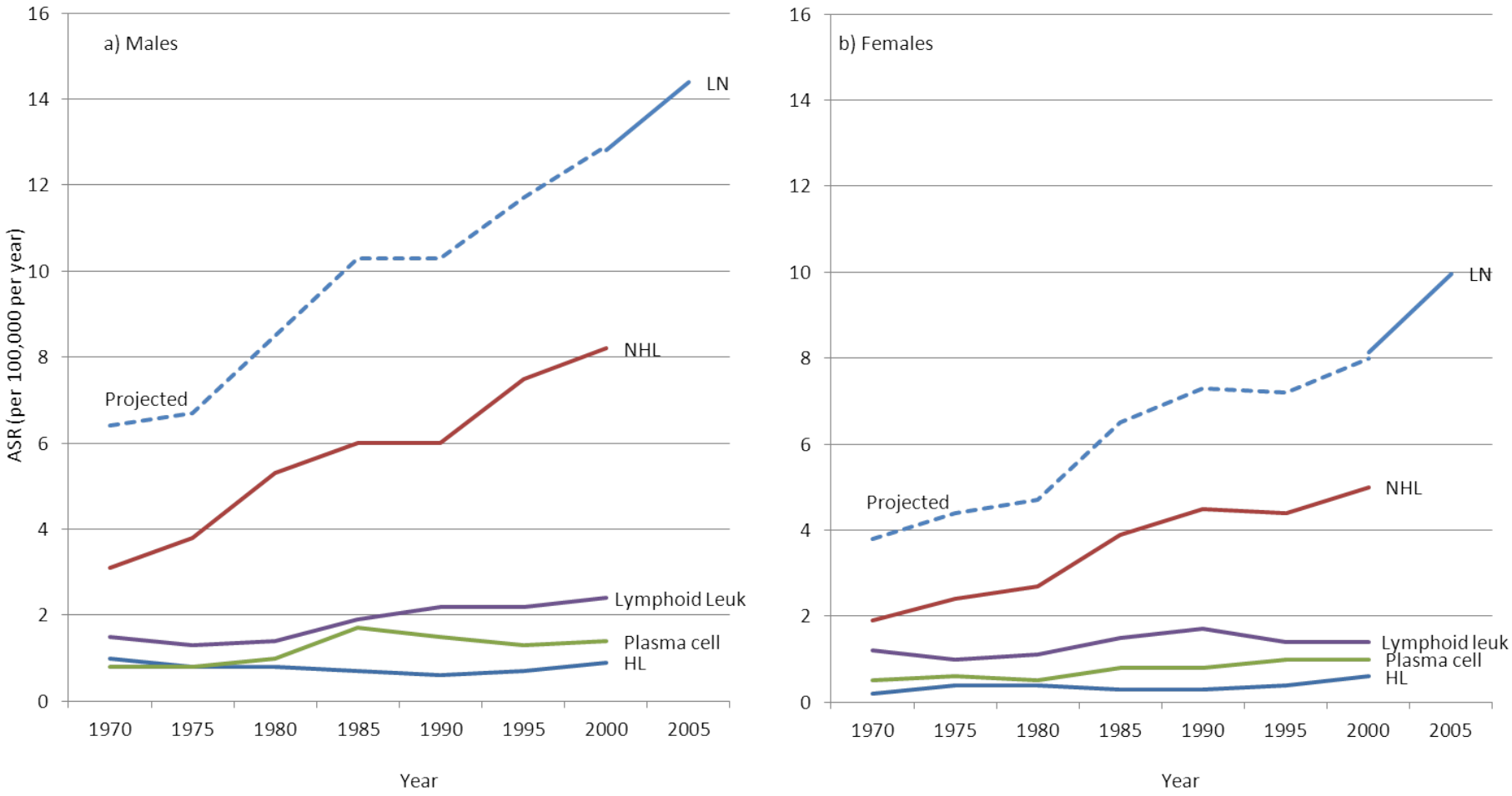
Table 1.8 Lymphoid neoplasms according to different age groups, 1998-2007. Source: Singapore Cancer Registry Report (NRDO 2010).

Age groups	Males			Females		
	Rank	% of all cancers in this age group	AAPC[a]	Rank	% of all cancers in this age group	AAPC[a]
0-14 years	3	14.9	+2.46	3	11.1	+9.66
15-34 years	1	21.1	+3.58	4	11.0	+6.26
35-64 years	6	6.3	+1.97	7	3.4	+4.18
65+ years	7	4.0	+2.42	7	3.6	+0.67
All age			**+2.37**			**+4.04**

[a] Average annual percent change, at 1998-2007.

Figure 1.4 shows the age-standardized rates per 100,000 per year by major subtypes of lymphoid neoplasms in Singapore. The incidence of NHL increased significantly from 1968 to 2002 in both males and females, while those of HL, plasma cell and lymphoid leukaemias remained stable across all years. Although these subtypes were all classified as lymphoid neoplasms based on the latest WHO classification, they behaved very differently across the years. It is important to understand the secular trends in order to provide clues to the underlying risk factors.

Figure 1.4 Age-standardized incidence rate (per 100,000 per year) by major subtypes of lymphoid neoplasms in Singapore, 1968-2007. Source: Singapore Cancer Registry Report (NRDO 2010)



LN, lymphoid neoplasms; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; Lymphoid Leuk, lymphoid leukaemia.

1.5 Aetiology of lymphoid malignancies

Two major factors that influence the incidence of cancer are hereditary and environmental factors. Hereditary factors are inherited from our ancestors and cannot be modified. Environmental factors, such as tobacco use, poor nutrition, inactivity, obesity, certain infectious or cancer-causing agents naturally occurring or existing as pollutants are potentially modifiable. The followings are the major environmental risk factors investigated in this thesis:

a) Occupational exposures

At present, no consistent pattern of causal relations between occupational agents and increased lymphoma risk exists (Alexander *et al.* 2007). Overall, studies on exposures based on occupational job title and industry have many limitations. Lack of specific individual-level exposure information is the main reason, and there were multiple-exposures in many occupations. Possible etiological agents suggested from literatures were teaching profession, chemical exposures e.g. organic solvents, pesticides and insecticides, exposure to fumes, textile or printing environment, and viral infection (Alexander *et al.* 2007; Boffetta & de Vocht 2007).

Teaching profession

Numerous studies examined the relation between the teaching profession and the risk of NHL (Baker *et al.* 1999; Boffetta & de Vocht 2007; Cano & Pollan 2001; Costantini *et al.* 2001; Ji & Hemminki 2006; Miligi *et al.* 1999; Svec *et al.* 2005; Zheng *et al.* 2002). Findings from a meta-analysis of 19

studies showed an elevated relative risk amongst teachers (RR 1.47, 95%CI 1.34-1.61) (Boffetta & de Vocht 2007). No difference in risk was observed between primary / secondary school teachers, theoretical or arts teacher, nor principals or headmasters in a Swedish cohort study (Cano & Pollan 2001). The detailed literature review on teaching profession and the risk of lymphoma is presented in **Chapter 5**.

b) Ultraviolet (UV) radiation

Solar UV radiation (wavelengths 100-400nm, divided into UV-A, UV-B and UVC) is a known carcinogen (El Ghissassi *et al.* 2009). UV-B is also crucial to humans as it is our major source of vitamin D which is produced in our skin upon sun exposure. There are several factors influencing UV radiation levels reaching Earth. These include geographical latitude and altitude, cloud cover, ozone level, seasons and time of day etc (Kimlin 2008).

Cartwright *et al* (1994) reported parallel increases in the incidence of both NHL and non-melanoma skin tumours in various populations using registry data from the IARC (Cartwright *et al.* 1994). Large population-based studies also observed an increased risk of subsequent NHL among patients with skin cancer, or vice versa (Adami *et al.* 1995; Hu *et al.* 2005). These findings led to the suggestion that solar UV irradiation may be a common risk factor, possibly through immunosuppression (Elwood & Jopson 1997). However in studies on individual-level sun exposures suggested an inverse association between sun exposure and risk of NHL, which may be explained by increased serum vitamin D level resulting from sun exposures (Hughes *et al.* 2004). The detailed literature review on sun exposure and the risk of lymphoma is presented in **Chapter 6**.

c) Alcohol drinking

Some epidemiological studies on alcohol drinking and risk of NHL have reported an inverse association (Kanda *et al.* 2009; Klatsky *et al.* 2009; Lim *et al.* 2007; Monnereau *et al.* 2008), others did not (Benedetti *et al.* 2009; Besson *et al.* 2006b; Chang *et al.* 2010b; Chang *et al.* 2004; De Stefani *et al.* 1998; Deandrea *et al.* 2007; Polesel *et al.* 2007; Tavani *et al.* 2001; Troy *et al.* 2010; Willett *et al.* 2007; Willett *et al.* 2004). The inverse relationships between alcohol drinkers and NHL risk were reported in moderate drinkers (Morton *et al.* 2005b) and wine drinkers only (Briggs *et al.* 2002b; Morton *et al.* 2003b); other studies showed no change in risk estimates in any types of alcoholic drinks (Morton *et al.* 2005b; Nieters *et al.* 2006). The detailed literature review on alcohol drinking and the risk of lymphoma is presented in **Chapter 7**.

d) Cigarette smoking

Tobacco smoke has been classified by WHO as carcinogenic to human (IARC 2012). Conflicting study on cigarette smoking were showing an elevated NHL risk (Freedman *et al.* 1998; Linet *et al.* 1992; Morton *et al.* 2005a; Talamini *et al.* 2005), while others reporting no association (Besson *et al.* 2006b; De Stefani *et al.* 1998; Fernberg *et al.* 2006; Herrinton & Friedman 1998; Monnereau *et al.* 2008; Nieters *et al.* 2008; Willett *et al.* 2004; Zahm *et al.* 1997). A large pooled analysis involving 6,594 cases and 8,892 controls, found a slightly elevated NHL risk with ever smokers (OR 1.07, 95%CI 1.00-1.15), and current smokers (OR 1.10 95%CI 1.00-1.20) (Morton *et al.* 2005a). Compared with non-smokers, heavy smokers and those who smoked for a longer duration had an increased NHL risk (Freedman *et al.* 1998; Morton *et al.* 2005a; Talamini *et al.* 2005).

Most of the studies on cigarette smoking consistently showed increased risk of HL (Besson *et al.* 2006a; Briggs *et al.* 2002a; Glaser *et al.* 2004; Hjalgrim *et al.* 2007; Nieters *et al.* 2006; Nieters *et al.* 2008; Willett *et al.* 2007). A meta-analysis of 17 studies reported an elevated risk of HL in current smokers (OR 1.35, 95%CI 1.17-1.56, p<0.001), but not former smokers (Castillo *et al.* 2011). The detailed literature review on cigarette smoking and the risk of lymphoma is presented in **Chapter 7**.

e) Other potential confounders and risk factors

Family history of cancer: An important familial component in the development of lymphoma has been reported in many studies. The risk of different LN differed according to gender and the familial relationship of the affected relative. A study from Swedish Family Cancer Database reported a 3-fold increase risk in developing HL in relatives of patients with HL (Goldin *et al.* 2004). In a separate study by InterLymph, they reported elevated NHL risk for individuals who had a brother with NHL (OR 2.8, 95%CI 1.6-4.8), a parent with HL (OR 1.7, 95%CI 1.0-2.9), or in women whose sister were diagnosed with leukaemia (OR 3.0, 95%CI 1.6-5.6) (Wang *et al.* 2007).

Social economic status (SES): Study on social economic status represents an indirect measure of known and unknown environmental risk factors. Education level is one of the contributing factors on the understanding of SES. Limited studies about educational level or other SES indicators and lymphoma risk have been published (Boffetta *et al.* 1989; Clarke *et al.* 2005; Hermann *et al.* 2010). In a large prospective EPIC cohort study, high education level (e.g. subjects with university degree) was positively related to women subjects diagnosed with B-NHL (HR 1.31, 95%CI 1.02-1.68); but

inversely to incidence of DLBCL (HR 0.46, 95%CI 0.27-0.79) (Hermann *et al.* 2010). In another study of 3,794 HL incidence from California cancer registry, using residential address to determine neighbourhood SES, high SES was associated with the risk of young HL (aged 15-44) (male: RR 1.22, 95%CI 1.05-1.42; female: 1.44, 95%CI 1.22-1.70), and the finding was consistent in Whites and Hispanic populations.

BMI/Obesity: Obesity, defined as ***body mass index (BMI) of 30kg/m^2 or above***, was associated with elevated risk of NHL incidence (Pan *et al.* 2005; Rapp *et al.* 2005; Willett *et al.* 2005; Wolk *et al.* 2001) in some studies but not in others (Britton *et al.* 2008; Chang *et al.* 2005; MacInnis *et al.* 2005; Willett *et al.* 2008). In a meta-analysis on 9 prospective studies, Renehan *et al* (2008) reported a weak positive association between 5 kg/m^2 increase in BMI and NHL incidence in both sexes (men: OR 1.06, 95%CI 1.03-1.09, p-trend<0.0001; women: OR 1.07, 95%CI 1.00-1.14, p-trend=0.05). Increased BMI at early adulthood was a better predictor variable than recent BMI (Kanda *et al.* 2010; Maskarinec *et al.* 2008; Pylypchuk *et al.* 2009).

In conclusion, lymphoid neoplasms are a group of complex disease more than 40 entities based on the latest classification in 2008, and there is a possibility of increasing subtypes in future due to the advance in genetic diagnosis. LN may be presented in any parts of the body, an extensive clinical investigations are needed to carry out in order to confirm a diagnosis. Disease progression depends on the subtype entities, as aggressive subtypes may present with signs and symptoms within weeks. Indolent entities may stay low or even asymptomatic for years, until it presents clinically or discovered by chance (**Figure 1.5**). Disease prognosis is usually good for NHL and HL as compared

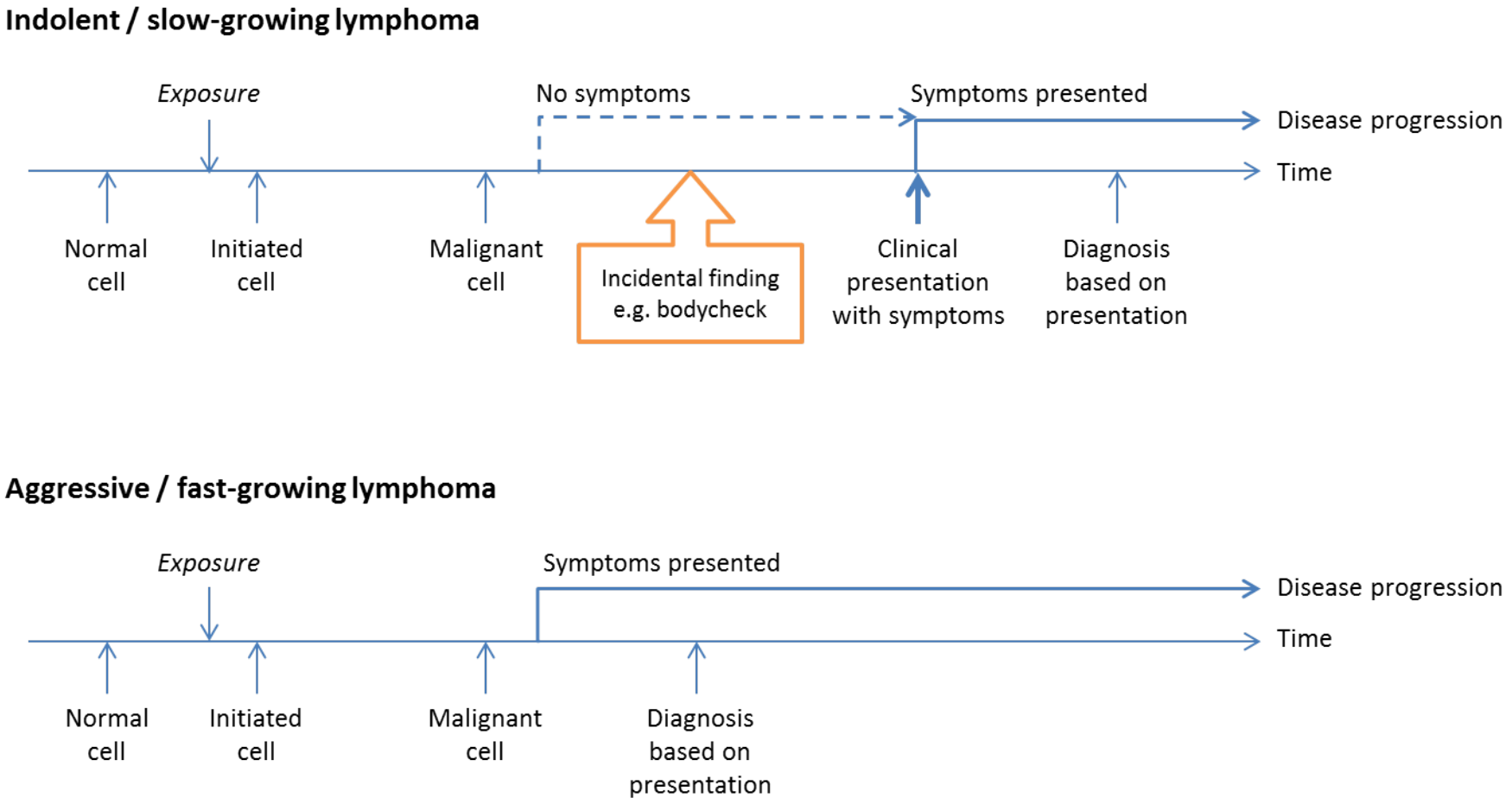
with the other cancers. Based on the subtypes of lymphoma, prognostic scores, stage of lymphoma at presentation, there are clinical guidelines for recommendation on standard treatment, such as chemotherapy, radiotherapy etc. *(National 2006a; National 2006b)*

The WHO classification of lymphoid neoplasms suggested both Hodgkin lymphoma and non-Hodgkin lymphoma are belonged to one big family. However, in terms of cancer rates across the world, clinical presentation and involvement (**Table 1.9**), response to treatment, as well as the etiological factors trigger the on-set of disease are different between HL and NHL. There are still a lot of questions about lymphoid neoplasms that need to be answered.

Table 1.9 Comparison of Hodgkin and Non-Hodgkin lymphomas (Emmanouilides & Casciato 2004)

Characteristic	**In Hodgkin lymphoma**	**In Non-Hodgkin lymphoma**	
		Low Grade	**Others**
Site of origin	Nodal	Extranodal (~10%)	Extranodal (~35%)
Nodal distribution	Centripetal (axial)	Centrifugal	Centrifugal
Nodal spread	Contiguous	Non-contiguous	Non-contiguous
CNS involvement	Rare (<1%)	Rare (<1%)	Uncommon (<10%)
Hepatic involvement	Uncommon	Common (>50%)	Uncommon
Bone marrow involvement	Uncommon (<10%)	Common (>50%)	Uncommon (<20%)
Marrow involvement adversely affects prognosis	Yes	No	Yes
Curable by chemotherapy	Yes	No	Yes

Figure 1.5 Schematic diagrams of disease progression for indolent and aggressive lymphoma



1.6 Aims of study and outline of thesis

The lymphoma rate in Singapore is the highest in Asia, and it is close to those of Western countries. It has been increasing consistently over the years with no apparent reasons to account for the rise. In **Chapter 1**, we presented the complex diagnosis of lymphoma, literature review on the different classifications adopted in the world in the past few decades, and the patterns of lymphoma incidence across countries. Since most of the studies on aetiology factors were conducted in the West, there is a knowledge gap regarding its association with the development of lymphoma in Asian populations. In **Chapter 2**, we provided an overview on the different study designs, with the strengths and limitations, and discussions on the best study design for the following studies. The aims of study in this thesis are :

1) To examine the trends of lymphoma in Singapore under REAL and WHO classification systems using the age-period-cohort analysis. In **Chapter 3**, using incidence data over 40 years from the national cancer registry, we decompose the individual effect of age, period and cohort on the secular trends of lymphoma in Singapore.

2) In order to understand the unique aetiology factors in Singapore, we conducted a hospital-based multi-ethnic case-control study, and presented its detailed study design and histological subtypes in **Chapter 4**. The aim of this hospital based case-control study is to:

   a. To provide an overall understanding of the associations of common occupations in Singapore with the risk of lymphoma, following the

Standard Singapore Occupation Classifications 2005 as described in **Chapter 5**.

b. To examine the effects of sun exposure for recreational and occupational purposes and related behaviours. In **Chapter 6**, we investigate the tropical sun effect on the risk of lymphoma as compared with previous studies conducted in temperate region.

c. To investigate the modifiable lifestyle factors of tobacco use and alcohol drinking behaviours in order to examine the link between lymphoma risk with these addictive behaviour. The details of this sub-study are described in **Chapter 7.**

Finally, in **Chapter 8**, we summarise the current knowledge about lymphoma, discuss the findings from our studies, highlight the strength and limitations of the studies, as well as provide an overall conclusion and suggest scope for future work.

Chapter 2

Overview of study designs

The basic purposes of epidemiological studies are to quantify the occurrence of disease or health-related issues, and to assess whether an exposure is associated with the diseases or outcome of interests in a population. It is never possible to design a research study without flaws, however, it is important for us to identify the strength and limitations, and select the best suitable design to answer our research questions.

2.1 Definition of terms

***Cases* –** an individual in a population presented with the disease, or undergo an event of interest. Cases may be identified through disease registries, hospital records, pathology reports, or even death certificates. The cases must comply with the standard definition for the study, e.g. first diagnosis of disease, or recurrent episodes of non-fatal condition etc. This numerator includes all cases in the study population at risk.

***Population at-risk* –** The denominator refers to the size of population at-risk of the event under investigation, and where the cases originates from, e.g. the catchment population of a hospital, the total population of a country etc.

Time period – Since most of the health-related event does not occur constantly over time, any measure of disease incidences shall be fixed at regular time period, to measure all cases arise from the population at risk, e.g. the number of colorectal, breast and prostate cancers were much lower at the beginning of Singapore Cancer Registry at 1968-1972 period than in 2003-2007(NRDO 2010).

2.2 Time trends of disease

Information on changes in cancer risk over time can generate etiological hypothesis or support suspected associations between risk factors and disease in a country. Using secondary data source, i.e. already existing dataset which routinely collected from data-collection system, provides a relatively fast and economical way of analysing data without the process of facing each disease subject.

The population-based cancer registry is an organization for the systematic collection and storage of all new cancer cases occurring, e.g. the Singapore Cancer Registry. They describe and report the cancer statistics displaying the nature of cancer burden in the population on every 5-yearly, it is also a resource for epidemiological studies. Cancer registry has a clear definition of catchment population of all new cases in the community. Information on incident cancer cases were collected through compulsory cancer notifications from all sections of the medical profession, pathology reports, hospital reports and death certificates (**Table 2.1**). We understand that notification is part of the clinical services, there may be cases missed to inform

during the process. The accuracy of cancer registration was increased by active reviewing of medical records at the hospitals and clinics and updating regularly. Cancer-specific incidence rates can be generated over the total population at-risk and reported in their statistical reports. International Classification of Diseases for Oncology (ICD-O) was used to code the topography and morphology of the tumours (Percy *et al.* 2000) (Appendix 2 and 3). The advantages of population-based cancer registry are the validity of data, but the database in cancer registry may have collected limited information on age, gender and ethnicity only.

Table 2.1 Sources of cases and types of notifications, 1998-2007 (Source: Singapore Cancer Report) (Chia *et al.* 2000; NRDO 2010; Seow *et al.* 2004)

	1993-1997		**1998-2002**		**2003-2007**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Cases notified by medical practitioners	**23339**	**(73.3)**	**27301**	**(71.0)**	**18680**	**(41.4)**
• Spontaneously	9551	(30.0)	15164	(39.4)	15928	(35.3)
• On request	13789	(43.3)	12137	(31.6)	2752	(6.1)
Cases registered by staff on the basis of	**8490**	**(26.7)**	**11146**	**(29.0)**	**26460**	**(58.6)**
• Pathology reports	6574	(20.7)	9075	(23.6)	23324	(51.7)
• Hospital records	1587	(5.0)	1717	(4.5)	2536	(5.6)
• Death certificate	329	(1.0)	354	(0.9)	600	(1.3)
TOTAL	**31829**		**38447**		**45140**	

On the other hand, **hospital-based cancer registries** record information on all cancer patients attended to a particular institution. They have readily accessible medical records on the patients with cancer, the treatments received and their outcomes. The purpose is to monitor and plan for patient care and resources allocation at hospital level. The advantage of hospital-based cancer registry is more extensive data collected than population registry, e.g. cancer

topography and morphology, TNM and staging, treatments, and number of admissions etc. However, no definite catchment population was in hospital settings, incident rates cannot be determined since the data only represent one hospital. They may also have limited access to the death certificates for the outcomes, and no standardized method of collection across all hospitals (dos Santos Silva 1999). Therefore, in order to compare the trends of cancer incidence in a country, population-based cancer registry is preferred than hospital-based.

2.3 Types of study designs

There are two basic approaches to assessing whether an exposure is associated with a particular outcome: by *experimental* or *observational* studies. The ***experimental*** or intervention approach refers to investigations carried out in laboratory environment, or randomized control trials on volunteer healthy subjects, with substance or various factors which they can control. For ethnical reasons, usually only experimental studies with potential benefits were conducted, which will not be focused on in this thesis. Most of the epidemiological studies conducted were ***observational*** studies, and will be discussed in the following.

Cohort study – Cohort study is a prospective observational study. It starts with a selection of population, i.e. a cohort, from a defined study base, and they are free from the disease of interest. The subjects are similar individuals but different with respect to certain exposure factor under study, and usually the exposure is few and limited. The information of exposure status is collected at

the beginning of cohort, follows over a long period of time for events to occur in this large group of people. Cohort study is used to estimate how this factor affects the average risk of certain outcomes or disease state, the incidence of the disease in the exposed individuals is compared with the incidence of the non-exposed group. The relative risk of disease is measured as the cohort remains at risk and under observation for the entire follow up time. For examples, the British doctor study by Sir Richard Doll is a cohort study from 1951 to 2001, on the analysis of association between tobacco smoking and risk of lung cancer (Doll *et al.* 2004).

Case-control study – Case-control study is a retrospective observation study. It starts with two groups of subjects with the presence or absence of disease state or outcome of interest, and determines the past exposure levels and their association with current disease status. This design allows the evaluation of a wide range of exposures that could be related to, or interacted with other factors and the disease of interest. A precise definition of cases is required for selection of eligible cases into this design, e.g. histological confirmation of cancers, and mainly recruited in hospital or clinic settings where patients attended. Controls should be selected from the same source population which give rise to the study cases, and they should be selected independently of their exposure status. Case-control study cannot yield estimates of effect as measures from cohort study, since the ratio of cases and controls are pre-determined and recruited by researchers, it estimated the incidence odds ratio. For example, the multi-country InterLymph study is a case-control study design, to assess multiple aetiology factors on the genesis of lymphoma in the West (Kricker *et al.* 2008; Morton *et al.* 2005a; Morton *et al.* 2005b).

Nested case-control study (Ernster 1994) – This is a specific group of case-control analysis conducted within a fixed cohort study. It begins with a defined cohort. Cases are cohort members who developed with the disease of interest after a certain follow-up period, and the controls are a sample of disease-free individuals at the time of selection, but not all members of the cohort. Time matching is essential for each case and control combination. For each case, a number of controls are selected based on several variables e.g. age, date of entry into cohort, length of time in cohort, or any other variables. Cohort members who serve as controls may later become a case.

2.4 Selection of controls

Wacholder *et al* have published a clear definition of selection of controls in case-control studies (Wacholder *et al.* 1992a; Wacholder *et al.* 1992b; Wacholder *et al.* 1992c). Two rules of thumb for selection of controls: 1) controls should be selected from same population which gives rise to cases, 2) controls should be selected independently of their exposure status of interest. Apart from nested case-control study that controls were arise from designated cohort population, other case-control studies do not have a clear and well-defined study base, therefore random selection from general population is not possible.

There are several sources of controls for population-based case-control studies. ***Neighbourhood controls*** refer to people living in the same neighbourhood; they are similar to cases in many aspects e.g. social economic status. It is time-consuming and expensive to draw a control to individually

match with cases on, for example, age, gender and ethnicity simultaneously. If the cases were being identified in a hospital which is related to specific exposure, then recruiting controls from the neighbourhood may introduce bias, since the exposure might not be the same. ***Friends or relatives controls*** are another source for individual matching with cases. Friends and their acquaintances may engage in similar activities and diet habit, or colleagues in the same occupational environment, which also related to the exposure of interest as cases, hence these may lead to overmatching in terms of exposures and other characteristics. ***Random-digit dialling****,* a method which is more commonly used in Western countries, offers researcher a cheap and efficient approach to the general population by a simple telephone call, especially if the area covered is huge. But this method is not suitable in Singapore since we do not have area code to identify the specific area we would like to make calls. There are also other limitations on this method that people may have more than one contactable telephone number, e.g. residential home phone, mobile phone, office phone lines etc. Residential phone line is not a must for every household, or it may be shared by several members of different age groups.

Hospital-based controls refer to a group of people who would be treated in a given hospital if they developed disease in question. If these 'hospital users' were came from the similar catchment area as the cases, and they were under the same referral patterns from primary physicians, they may be the same pool of patients that give rises to cases. Comparatively these hospital controls are easy to be identified, they also experienced illness and hospitalization, they may resemble the cases with respect to similar area of residence, tendency to answer questions, and have less biased estimates to recall differently from cases. The major problem for hospital controls is their illness may share risk factors with cases, and the possibility of over or under

represent the exposure distribution in the source population. Limiting the admission diagnosis for controls in conditions associated with cases, and select controls with various different conditions may cancel out the bias introduced by specific diseases.

2.5 Bias and confounding factors

Bias is defined as systemic errors in the design or conduct of a study, the observed study results will tend to be different from the true results. On the other hand, confounding factors are risk factors correlated with the exposure under study, and it must be also an independent risk factor for the disease, but not an intermediate factor in the casual pathway between exposure and the disease. The presence of confounding factors will obscure the real effects between the exposure and the outcome of interest (Szklo & Nieto 2004).

Selection bias occurs when there is a difference between the characteristics of the people selected in the study, and those who did not participate, due to improper procedure of acquiring persons from the target population into the study. It results in a distortion in a measure of association. For example, when the exposure of interest are related to the conditions for controls to be hospitalized, and at the same time with the disease of study, thus the association will biased towards null. This is known as the Berkson's bias in hospital-based case-control study infamously. Self-selection is also a bias, when people who volunteer to participate in a study tend to be different from the non-responders, in terms of demographic and lifestyle factors (e.g. more health conscious or with better education), which could be the risk factors for outcome

of interest. Healthy worker effects are another bias in occupational exposure studies. When cases are workers, controls should also be workers in order to compare occupational-related exposures, since working individuals are generally healthier than people who are not (fit for) working. In a nutshell, differential recruitment criteria for cases and controls, or individual hospitalized for disease related to exposure under investigation should be excluded to eliminate selection bias (dos Santos Silva 1999).

Measurement (information) bias occurs when there are errors in measurement, e.g. interviewer bias, the interviewer probe the respondents differently due to their disease status. A standard operating procedure should be administrated, and with trainings provide for interviewers to maintain the quality since the disease states of cases and controls cannot be blinded in a hospital-based case-control setting. The questionnaire should also be standardized and administrated to all participants, the quality assurance should follow through from the beginning to the end of study, e.g. using of voice recording device to maintain the standard. Recall or reporting bias is another kind of information bias, where the cases and controls recall differently on the exposure of interest. When cases and controls are both hospitalized patients, they experienced the similar referral pattern, thus will reduce the discrepancy between cases and controls on recalling past exposures.

In order to control for confounding factors, it is best to do this in the design phase, rather than in the analysis phase. Randomization is the gold standard method in experimental studies, i.e. randomized control trials. Restriction on inclusion criteria is a convenient but efficient way to control for

strong confounding factors, however the restricted variables cannot be assessed for confounding in the subsequent analysis. Matching is another method to constraint the distribution of confounding variables within cases and controls are similar, e.g. age, gender, race, social economic status. The matched variables are also cannot be assessed for effect estimation.

2.6 Conclusion

In conclusion, there are several factors need to be considered in designing a study for investigations on a rare disease such as lymphoma:

(1) In order to investigate the trends of lymphoma in Singapore, the population-based cancer registry provided a highly valid data source, which came from a defined population at-risk in the country. Age-standardized rates can be calculated across the periods and compared with other countries;

(2) The advantage of nested case-control study is that both cases and controls arise from a defined cohort population, where in case-control study that is not easily defined. Smaller number of study subjects are needed for analysis than cohort study, thus it is less expensive and less time consuming. This is particularly important for expensive laboratory analysis with limited amount of samples collected. Data are likely collected prior to diagnosis of disease than conventional case-control study, hence recall bias is not an issue. Nested case-control study consists of both the robustness of cohort study, and the ability to assess multiple exposures as case-control

study. It would be a perfect choice to investigate aetiology factors of rare disease as lymphoma, if such a cohort is existed. In the Singapore context, we would be able to ascertain cases from the Singapore Cancer Registry, however we still need to recruit controls from the general population.

(3) Regarding the aetiology factors investigation, a hospital-based case-control study design would be appropriated, based on the biology of disease, long duration of exposure and long period of time for lymphoma to accumulate. It requires smaller sample size in case-control design than cohort studies and thus more cost-effective.

(4) The referral pattern from primary physicians to generalized hospitals for further investigations and treatments are the same in Singapore, regardless the admission is related to cancer or any other clinical diseases, and they are usually come from the catchment area of the nearest hospital. Thus the Berkson's bias would be reduced.

(5) There were no known risk factors to explain for lymphoma, no vaccines available at the market to prevent lymphoma, no health programmes offered on how to prevent lymphoma, nor screening programme offered by any clinic or hospitals at the time being. Most of the general population have no idea about the cause of lymphoma in Singapore; differential reporting in information bias may not be a concern.

(6) Quality assurance procedures should be implemented to reduce bias and confounding factors in the study design. Standard operating procedures for recruitment should be adhered to by trained-interviewers, including inclusion and exclusion criteria for cases and controls. The interviewer shall follow the standardized questionnaire throughout the study.

(7) Since the population is dynamic and it is difficult to define the population at-risk, hospital controls should be time-matched with cases by recruitment of controls that are still at-risk at each time a case is diagnosed. Matching on strong confounding factors such as age and gender would increase precision and lower the cost by recruiting a relatively lower sample size.

(8) In the analysis phase, adjustment for known confounding factors would remove the effect from confounding factors, and may remove the related unknown risk factors.

Chapter 3

Trends of lymphoma in Singapore from 1968-2007

The age-period-cohort (APC) modelling is often used to examine the temporal variations in disease incidence and typically of chronic diseases (Clayton & Schifflers 1987), e.g. primary bone cancer incident rate in the United States (Anfinsen *et al.* 2011), gastric cancer mortality in Europe (Malvezzi *et al.* 2010). The time trend of disease rates is attributed by the effects of a) chronological age at diagnosis, b) period or year of diagnosis, c) cohort or the year in which an individual is born (Holford 1991). The chronological age effect suggests the different risks associated with time since birth. The predominance of period effect suggests a change in a particular calendar year of diagnosis which affects all age groups, e.g. change in method of diagnosis or disease classification system. Lastly, the birth cohort effect suggests differences between distinct generations (birth cohorts) of individuals in the population, i.e. a change in lifestyle or prevalence of an infectious disease over a lifetime.

3.1 Source of data

This is a retrospective population-based study, using aggregated unidentified data requested from the Singapore Cancer Registry, in January 2008 for the period 1968-2002. Further updates on the data for the duration 2003-2007 was obtained in September 2010. The Singapore Cancer Registry is a well-documented registry since 1968. It receives cancer notification mainly from the medical profession, as well as review from pathology reports, hospital

records and occasionally death certificates. The data is managed by the National Registry of Diseases Office, Singapore. The completeness of cancer reporting was close to 100% since 1990 (NRDO 2010). The histological grading of lymphoma was classified by ICD-9 for the period of 1968-1992, ICD-O-2 for 1993-2002, and ICD-O-3 for 2003-2007. The lymphoma data was presented in 5-yearly age intervals (0-4, 5-9 to 75-79, and 80+ years) and for the periods (1968-1972, 1973-1977, 1978-1982, 1983-1987, 1998-2002, and 2003-2007).

Statistics of the Singapore population (i.e. denominators) for the period 1968 to 2007 were obtained from the Department of Statistics. These were derived by interpolation using the 1970, 1980, 1990, and 2000 census data, and extrapolation for 1968 to 1970 and 2001 to 2007. The denominator was presented in 5-yearly intervals (0-4 to 80+ years) using the same calendar period (1968-1972 to 2003-2007).

3.2 Statistical analysis

a) Age-standardized rates of lymphoid neoplasms

The LN incidence was grouped in 5-yearly intervals for both age at diagnosis (0-4 to 80+ years) and calendar year of diagnosis (period) (1968-1972 to 2003-2007), and stratified by gender. The age-standardized rate were calculated by direct standardization according to the World Standard Population (Segi 1960) and was expressed per 100,000 person-years. The age-standardized incidence rate across periods was plotted separately by gender.

b) Age-specific rates of lymphoid neoplasms

The 5-yearly age-specific rates of lymphoid neoplasms were calculated using the incident cases of LN as numerator, and the Singapore population at the respective age range as denominator. The age-specific rates were presented per 100,000 person-years. The age-specific temporal trends were plotted for both year of diagnosis (period) and of birth cohort according to gender. For the clarity of presentation, only subjects aged 15-79 years were plotted.

c) APC modelling by maximum likelihood approach

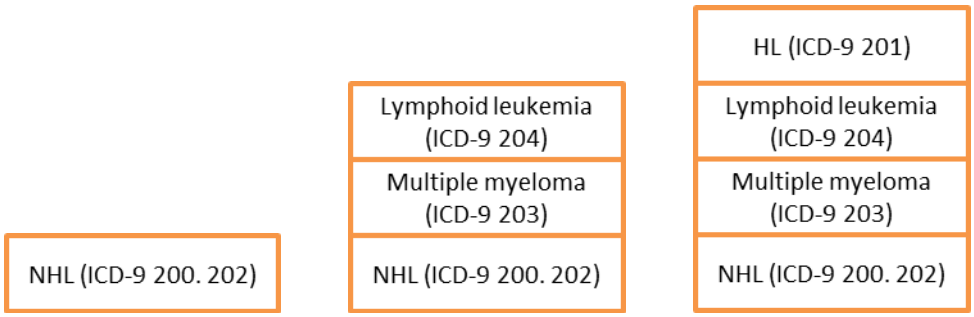
Due to the complexity and changes in lymphoma classifications in the past few decades, the subtypes of lymphoma included in each analysis varies across publications. We generated 3 different models to compare age, period and cohort effects, to take into account the changes in classification system. Considering that the paediatric cases may behave differently from the rest of adult lymphoma cases, and the open-ended oldest group (i.e. aged 80 years and above) may have limited cases and hence resulted in unstable estimates, both these groups were excluded from APC analysis. Thus these APC models included only subjects aged 15 to 79 years, for the period 1968 to 2007:

- ***Model 1 – NHL***: This is based on the classification of Non-Hodgkin lymphoma as in most of the previous publications. Traditional NHL included diffuse and follicular lymphoma, marginal zone B-cell lymphoma and T/NK-cell lymphomas only (ICD-9 codes 200, 202).

- ***Model 2 – B-/T-cell NHL*** : This NHL model is based on the WHO classification of B-cell neoplasms and T/NK-cell neoplasms (Jaffe *et al.* 2001). This model includes Model 1 of traditional NHL, plasma cell tumours and immunoproliferative neoplasm (ICD-9 203 / ICD-O 9731-9734 and 9760-9768), and precursor lymphoid leukaemia and chronic lymphoid leukaemia (ICD-9 204 / ICD-O M9727-9729, 9820-9837).

- ***Model 3 – WHO LN*** : This model is based on the WHO classification of lymphoid neoplasms. This includes NHL from Model 2 with Hodgkin lymphomas cases (ICD-9 201 / ICD-0 9650-9667).

Figure 3.1 Schematic diagrams of Models 1 to 3.



Model 1 NHL **Model 2 B/T-cell NHL** **Model 3 LN**

To obtain the effects of age, period and cohort, a log-linear model was fitted to the data using Poisson regression with a log link function, and adjusted for gender in all models.

The general form of the age-period-cohort model is

$$\log(I_{ijk}) = \mu + \alpha_i + \beta_j + \gamma_k + \varepsilon_{ijk}$$

where I_{ijk}= the incidence rate in the i^{th} age group, j^{th} period and k^{th} cohort, μ = the intercept, α_i = the effect of the i^{th} age group (i=1,2…I), β_j = the effect of the j^{th} period (j=1,2…J), γ_k = the effect of the k^{th} birth cohort (k=I-i+j), and ε_{ijk} = random error term. The model fitting was based on 13 age groups (15 to 79 years), 8 periods (1968-2007) and 20 birth cohorts (1891-1895 to 1986-1990). The first calendar period in 1968-1972, the middle age group of 40-44 years as well as birth cohort 1941-1945 were used as reference groups.

We used the model building approach suggested by Holford (1991). For each classification, the following models were generated: a one-factor ***age*** model, two-factor ***age-drift***, ***age-period*** and ***age-cohort*** models and full 3-factor ***age-period-cohort*** model. The first model with only *age* assumes no temporal variation, and that chronic disease incidence takes time to accumulate as people age. The two-factor *age-drift* model refers to regular drift which cannot be attributed to period or cohort influences.

Likelihood ratio tests were carried out on nested models to assess the significance of added effects. The effects of these risk factors were quantified using estimates obtained from the best fitting log-linear model. We compare the one-factor model with the two-factor models. The age-drift model was then compared specifically with age-period and age-cohort model separately.

Subsequently the comparisons of each two-factor model were made with the full 3-factor model. Since the 3 components are interrelated, there is an exact linear dependency between the age, period and cohort. To overcome this identifiability problem, we constrained the first two calendar-year periods as identical i.e. replacing the period of 1973-1977 with 1968-1972, assuming the incidence rates of the first 2 periods were the same (Holford 1991).

The deviance statistics was used to determine the goodness-of-fit of the models and significance of the effects (Clayton & Schifflers 1987). A low deviance and a non-significant p-value in the test indicate a good fit of the model to the data. In addition, we further estimated the residual deviate from linear regression of the full APC model as these estimates were identifiable and invariant. The non-linear deviates for each factor in the full APC model were known as the curvature and plotted by age, period and cohort factor separately. All statistical analysis was performed using R 2.8.1 statistical software package, assuming a two-sided test at the 0.05 level of significance.

3.3 Lymphoma incidence from 1968 - 2007

From 1968 to 2007, a total of 8,903 (5,261 males, 3,642 females) lymphoid neoplasms were recorded in the Singapore Cancer Registry for cases aged 0 to 80+ years **(Table 3.1)**. There were 262 cases in males and 157 cases in females for the period 1968-1972, then it increased to 1,309 and 974 cases in males and females respectively between 2003 and 2007. The number of lymphoid neoplasms cases was presented according to 4 major subtypes, including Precursor, Plasma cell myeloma, HL, and the rest of NHL in **Figure**

3.2. The major group of NHL subtypes increased dramatically, while HL, plasma cell and precursor subtypes rose gradually over the 40–year period.

As presented in **Figure 3.3** the age-standardized incidence rates (ASR) of lymphoid neoplasm increased from 5.08 per 100,000 per year (6.37 in males, 3.82 in females) in 1968-1972, to 11.89 per 100,000 per year (14.06 in males, 9.92 in females) in 2003-2007. HL rates were relatively stable across the four decades, while NHL rates rose steadily. In terms of gender difference, the ASR in males across all periods was consistently higher than females, and ranged from 1.39 to 1.69:1 (**Table 3.1**).

Age-specific incidence rate of LN among age 15 to 79 years

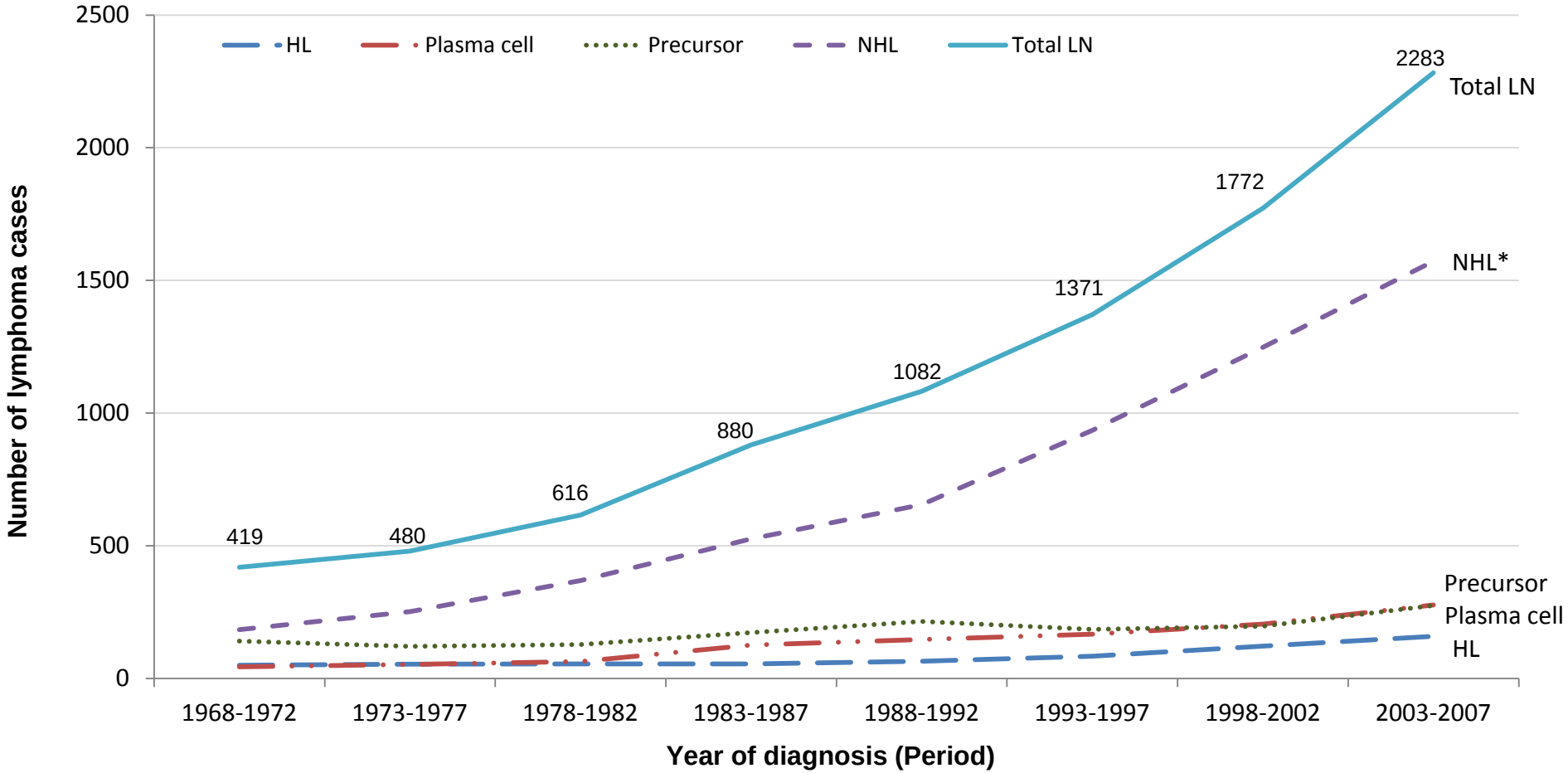
The log-scaled age-specific incidence per 100,000 person-years of LN was plotted by calendar period and birth cohort in **Figure 3.4**. For clarity of presentation, only data for every other 5-year age group are shown for age between 15 to 79 years.

Within each age group, the incidence rate of LN increased with each successive calendar period. Within the same calendar period, the incidence rates increased with age, particularly in those over 40 years old. The pattern was consistent across all calendar periods, with the highest rates being observed in the oldest age group. Likewise, the parallel age-specific curve showed increasing incidence with each successive birth cohorts. This same pattern was observed for both genders, as shown separately for calendar period in **Figure 3.5** and birth cohort in **Figure 3.6**. The incidence rates in males were consistently higher than females.

Table 3.1 Lymphoid neoplasms according to subtypes and gender, 1968-2007. (Source: Singapore Cancer Registry)

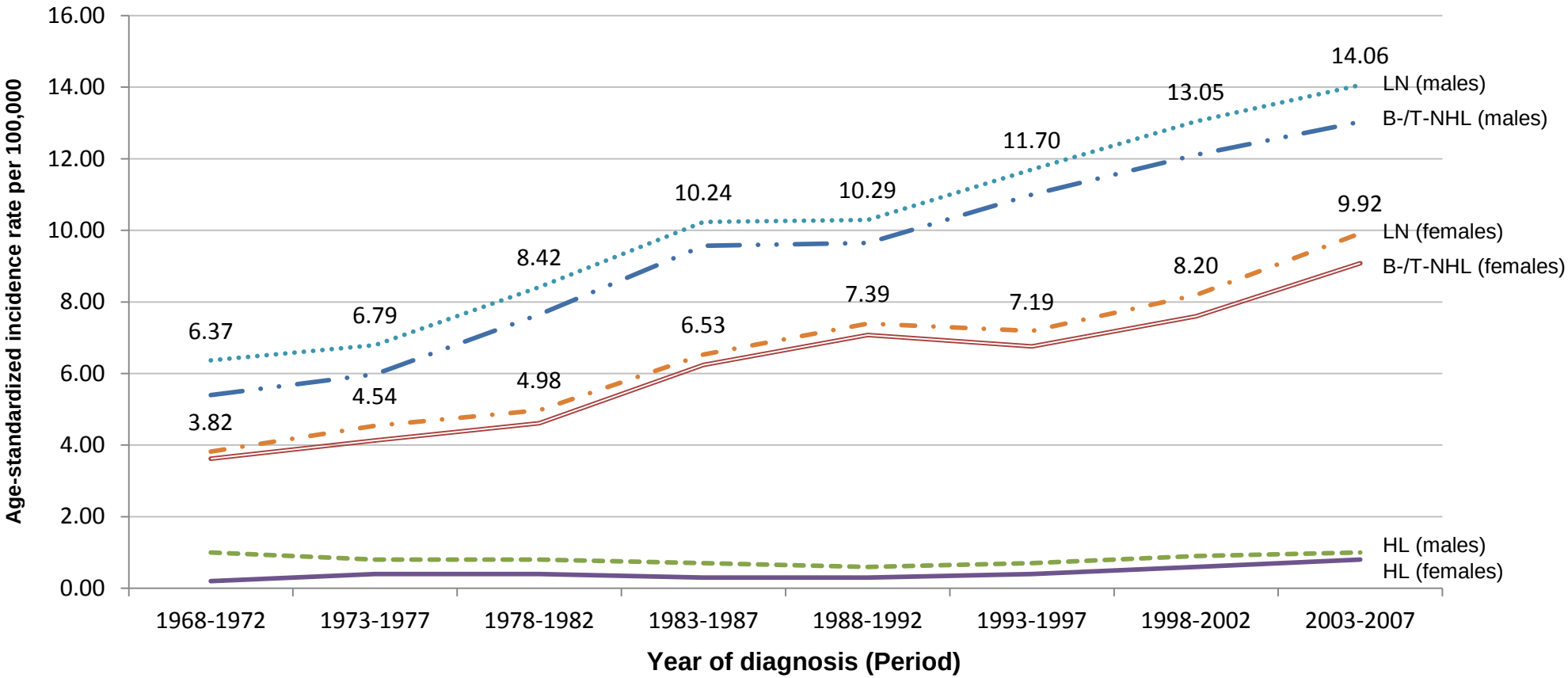
	Histological subtype (ICD coding)	Period								
		68-72	73-77	78-82	83-87	88-92	93-97	98-02	03-07	TOTAL
Males										
ICD-9-CM	• Lymphosarcoma and reticulosarcoma (200)	106	116	136	186	188				
	• Hodgkin's disease (201)	42	36	36	37	41				
	• Other malignant neoplasm of lymphoid and histiocytic tissue (202)	9	37	97	128	182				
	• Multiple myeloma and immunoproliferative neoplasm (203)	25	28	40	79	84				
	• Lymphoid leukaemia (204)	80	71	73	97	125				
ICD-O	• Malignant lymphoma, NOS (9590/3)						91	96	41	
	• Non-Hodgkin lymphoma, NOS (9591/3, 9593/3, 9595/3, 9672/3)						39	52	40	
	• Hodgkin lymphoma (9650/3-9667/3)						52	71	95	
	• B-cell lymphoma (9670/3-9698/3, 9760/3-9761/3, 9823/3,9826/3, 9940/3)						374	478	665	
	• T- and NK-cell lymphoma (9700/3-9717/3, 9827/3)						67	120	168	
	• Plasma cell myeloma (9731/3, 9732/3, 9830/3)						87	111	151	
	• Precursor lymphoid leukaemia (9727/3-9729/3, 9820/3-9821/3)						112	123	149	
	TOTAL incidence	**262**	**288**	**382**	**527**	**620**	**822**	**1051**	**1309**	**5261**
	Age Standardized Rate per 100,000	6.37	6.80	8.42	10.24	10.29	11.71	13.05	14.06	
Females										
ICD-9-CM	• Lymphosarcoma and reticulosarcoma (200)	61	69	74	126	166				
	• Hodgkin's disease (201)	8	18	19	18	24				
	• Other malignant neoplasm of lymphoid and histiocytic tissue (202)	8	30	62	86	119				
	• Multiple myeloma and immunoproliferative neoplasm (203)	19	25	24	47	63				
	• Lymphoid leukaemia (204)	61	50	55	76	90				
ICD-O	• Malignant lymphoma, NOS (9590/3)						65	62	21	
	• Non-Hodgkin lymphoma, NOS (9591/3, 9593/3, 9595/3, 9672/3)						21	39	24	
	• Hodgkin lymphoma (9650/3-9667/3)						32	51	64	
	• B-cell lymphoma (9670/3-9698/3, 9760/3-9761/3, 9823/3,9826/3, 9940/3)						250	338	512	
	• T- and NK-cell lymphoma (9700/3-9717/3, 9827/3)						26	62	101	
	• Plasma cell myeloma (9731/3, 9732/3, 9830/3)						80	95	126	
	• Precursor lymphoid leukaemia (9727/3-9729/3, 9820/3-9821/3)						75	74	126	
	TOTAL incidence	**157**	**192**	**234**	**353**	**462**	**549**	**721**	**974**	**3642**
	Age Standardized Rate per 100,000	3.82	4.54	4.98	6.53	7.39	7.20	8.20	9.92	
	TOTAL NUMBER OF INCIDENCE	**419**	**480**	**616**	**880**	**1082**	**1371**	**1772**	**2283**	**8903**
	Male-to-female ratio on ASR	**1.67**	**1.50**	**1.69**	**1.57**	**1.39**	**1.63**	**1.59**	**1.42**	

Figure 3.2 Number of lymphoid neoplasms cases by 4 major subtypes, 1968-2007. (Source: Singapore Cancer Registry)



*__NHL__ includes including diffuse large B-cell lymphoma (incl. Burkitt); follicular lymphoma; B-cell SLL; marginal zone lymphoma; Hairy cell leukaemia; B-cell lymphoma, NOS; mycosis fungoides/Sézary syndrome; peripheral T-cell lymphoma; cutaneous T-cell lymphoma and T-cell lymphoma, NOS (i.e. classification in model 1).

Figure 3.3 Age-standardized incidence rates of lymphoid neoplasms in Singapore by gender, 1968-2007.



Rates adjusted to World Standard Population for subjects aged 0 to 80+ years.

HL – Hodgkin lymphomas only; **B-/T-cell NHL** – classification as defined in Model 2, including B-cell Precursor (include. ALL),diffuse large B-cell lymphoma (incl. Burkitt); follicular lymphoma; B-cell chronic lymphatic leukaemia (incl. SLL); marginal zone lymphoma; Hairy cell leukaemia; multiple myeloma/plasmacytoma; and B-cell lymphoma, NOS; T-cell ALL (incl. ALL + adult T-cell leukaemia); mycosis fungoides/Sézary syndrome; peripheral T-cell lymphoma; cutaneous T-cell lymphoma; T-cell lymphoma, NOS; **LN** – classifications as defined in Model 3 (NHL + HL).

Figure 3.4 Age-specific incidence rates of LN by period and birth cohort, 1968-2007.

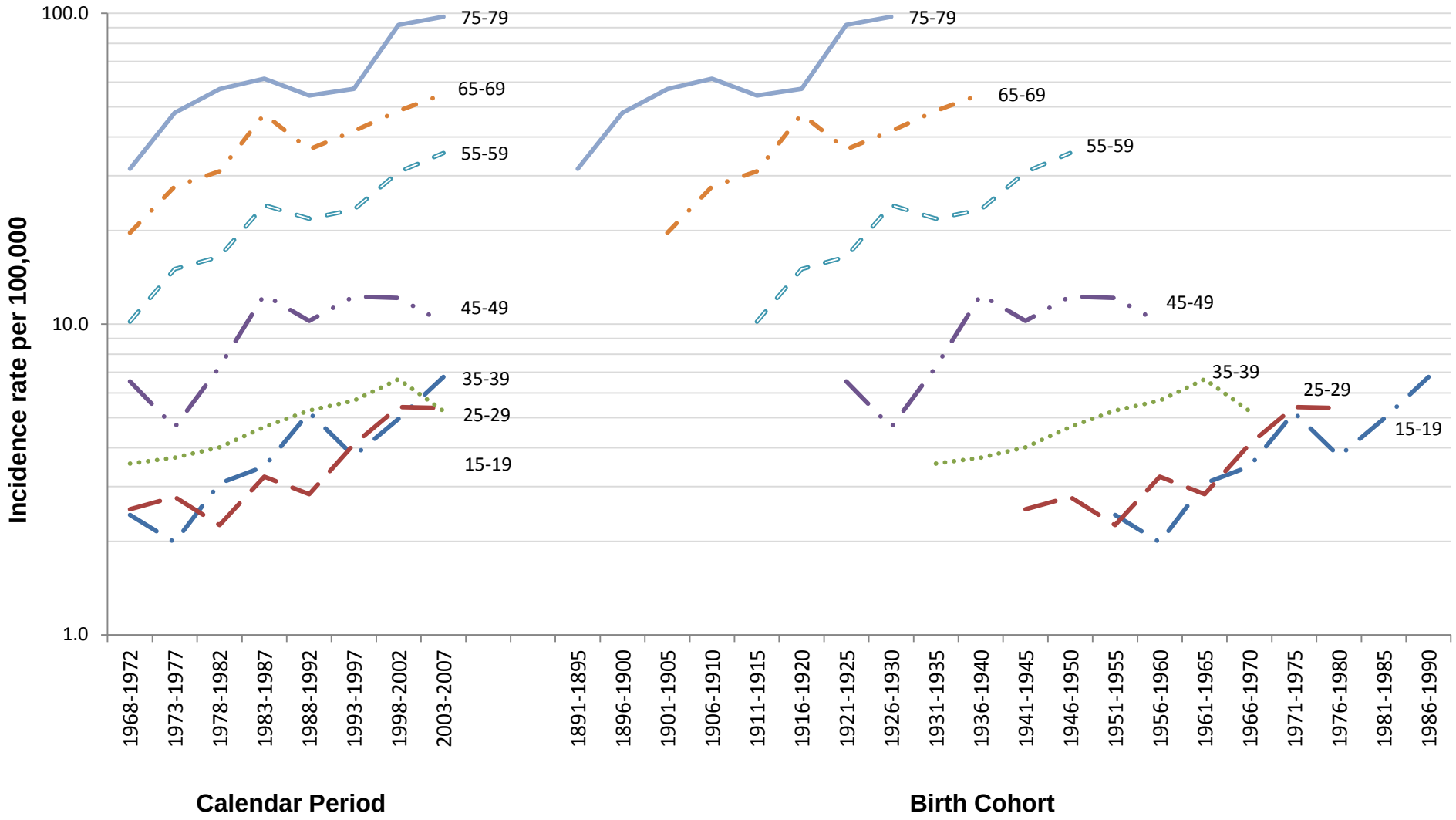


Figure 3.5 Age-specific incidence rates of LN by calendar period and gender, 1968-2007.

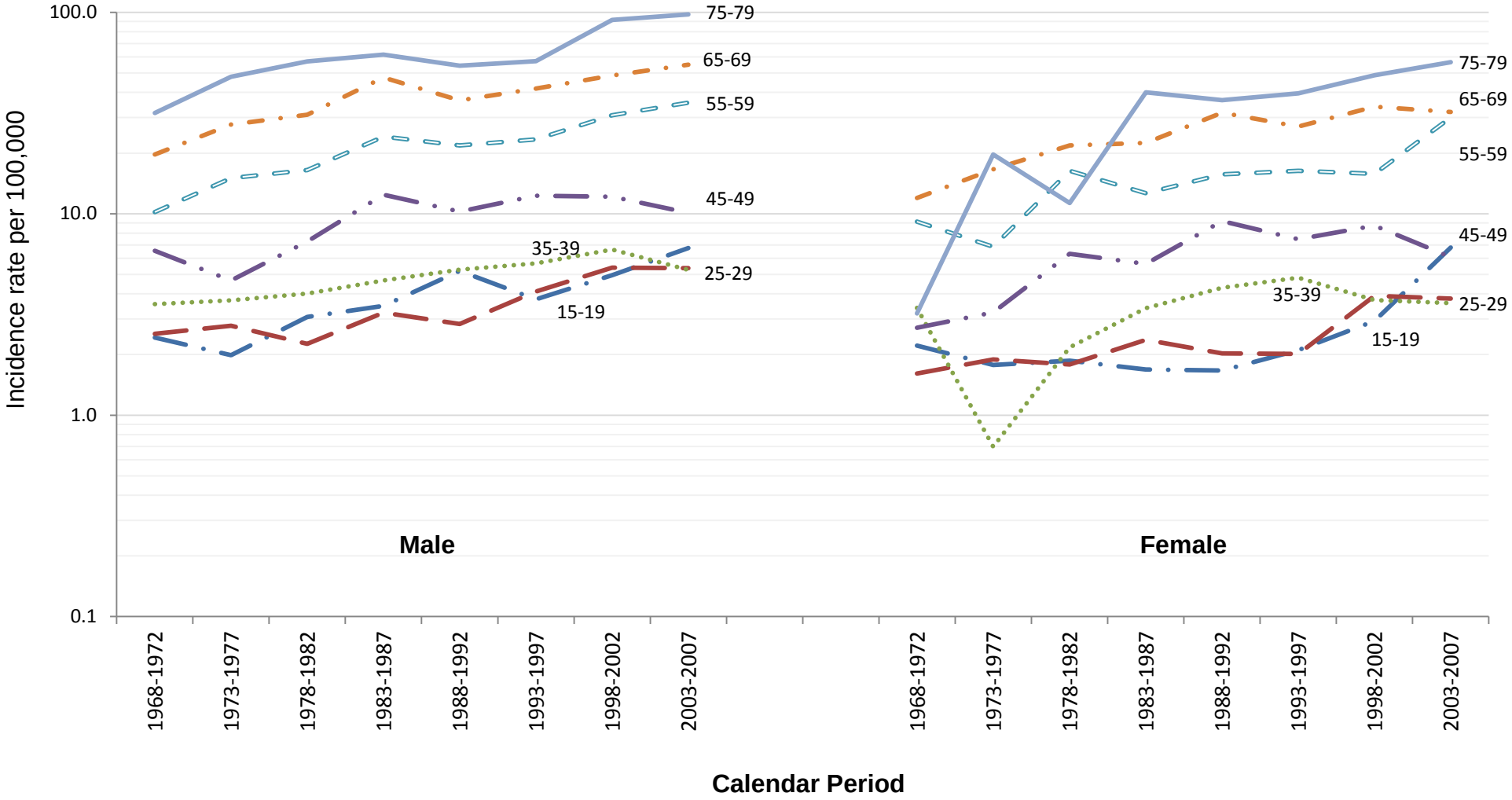
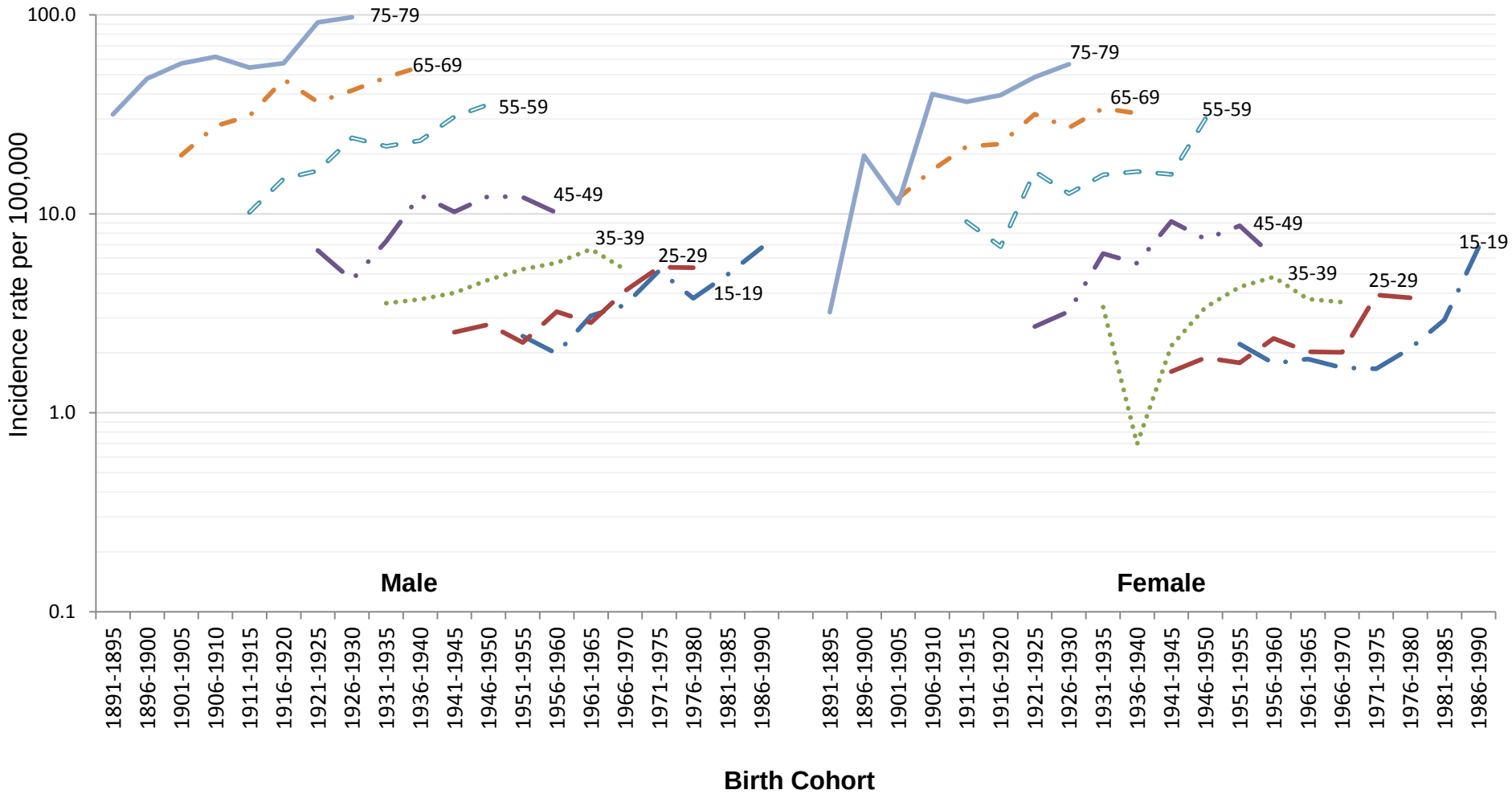


Figure 3.6 Age-specific incidence rates of LN by birth cohort and gender, 1968-2007.



3.4 APC modelling

Model 1: APC modelling of NHL using traditional classification

Using NHL definition of previous publications (ICD-9 200, 202), restricting age of subjects to between 15 to 79 years for the APC modelling, there were 5,058 cases (3,014 males and 2,044 females) in this analysis. The models with Age-Period (AP), Age-Cohort (AC) and full Age-Period-Cohort (APC), all adjusted for gender, showed good fit with $p>0.05$ (**Table 3.2)**. However, the full APC model showed the smallest deviance of 182.1 with 169 degree of freedom ($p=0.232$), with all variables (age, period, birth cohort and gender) achieving statistical significance, and no residual over-dispersion found.

Using the likelihood ratio test for model comparisons, both period and cohort effects showed significant improvement in the fit of model, in addition to age effect alone. Comparing models AP and APC, we concluded that the cohort effect was statistically significant (Δdeviance=33.38 on 18 degrees of freedom, $p=0.015$) after adjusting for age, gender and period effect. Likewise, comparing models AC and APC, we found that the effect of calendar period is significant (Δdeviance=13.31 on 6 degrees of freedom, $p=0.038$) after adjusting for age, gender and cohort effects. The results indicated both period and cohort played a significant role in the development of NHL for both men and women over the years. A similar result was found when comparing models AD with AP and AC respectively.

Model 2: APC modelling of B/T-NHL

With the addition of plasma myeloma and CLL subtypes in the definition of NHL based on the updated WHO classification system, there were 6,635 NHL cases (3,917 males and 2,718 females) included in this model. The results of APC modelling for Model 2 were very similar to Model 1 (**Table 3.2**). Models with AP, AC and full APC showed good fit ($p>0.05$). All the variables (age, period, birth cohort and gender) were statistically significant, and no residual over-dispersion was found. The full APC model resulted in the smallest deviance of 177.5 with 169 degree of freedom ($p=0.312$).

Using the likelihood ratio test for model comparisons, including both period and cohort effects, in addition to age effect, significantly improved the fit of model. By comparing models AP with APC, the cohort effect after adjusting for age, gender and period was statistically significant (Δdeviance=33.78 on 18 degrees of freedom, $p=0.013$). Likewise, comparing models AC with APC, we found that, after adjusting for age, gender and cohort effects, the effect of calendar period is significant (Δdeviance=14.76 on 6 degrees of freedom, $p=0.022$). The results indicated both period and cohort played a significant role in the NHL for both men and women over the years. A similar result was found when comparing models AD with AP and AC respectively.

The effect estimates from the full log-linear APC regression model were plotted in **Figure 3.7**. The reference points used were the mid-point of age groups at 40-44 years and birth cohort at 1941-1945, and the starting of calendar period 1968-1972. The age, period and cohort effects were all increasing steadily, with age effects presented with the steepest slope.

Figure 3.8 showed the curvature effects of age, period and cohort from the full APC model under this classification. Large curvature for the age effect suggested departure from linear age trend. With age 40-44 years as the lowest point, positive deviation was observed below age 20 years, and age 55 years and above. Curvature was minimal for period effect, indicating slight deviations of period estimates from a linear periodic trend. The departure of cohort from linear cohort trends suggested a strong cohort curvature effect among people who were born between 1906 and 1951.

We have also tested for interactions between gender and age, period or cohort effects (i.e. age-gender, period-gender and cohort-gender interactions). None of the interaction terms were significant indicating the APC models do not differ according to gender.

Model 3: APC modelling of LN

In Model 3, we included the HL cases with NHL, since they were broadly classified as lymphoid neoplasms according to WHO classification. There were 7,217 cases in Model 3 (4,284 males and 2,933 females) aged between 15 and 79 years **(Table 3.2)**.

All the variables (age, period, birth cohort and gender) were statistically significant, and no residual over-dispersion was found. By comparing models AP with APC, we observed that, after adjusting for age, gender and period effect, cohort effect was statistically significant (Δdeviance=48.92 on 18 degrees of freedom, $p<0.0001$). However, the period effect did not improve the fit of the model (Δdeviance=9.34 on 6 degrees of freedom, $p=0.156$) after adjusting for age, gender and cohort effect. After HL was added into the model, the period effect disappeared.

We have also tested for interactions between gender and age, period, or cohort effects (i.e. age-gender, period-gender and cohort-gender interactions). None of the interaction terms were significant indicating the APC models do not differ according to gender.

Table 3.2 Summary of goodness-of-fit and likelihood-ratio test statistics of APC analyses.

	Model 1: NHL			Model 2: B-/T-cell NHL			Model 3: LN		
	Female	**Male**	**Total**	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
Number of cases (age 15-79 years)	2,044	3,014	5,058	2,718	3,917	6,635	2,933	4,284	7,217
Terms in model**	**Deviance***	**df**	***p*-value[§]**	**Deviance***	**df**	***p*-value[§]**	**Deviance***	**df**	***p*-value[§]**
Age (A)	645.4	194	<0.001	615.2	194	<0.001	652.5	194	<0.001
Age + Linear Drift[‡] (AD)	234.7	193	0.022	231.1	193	0.032	244.0	193	0.008
Age + Period (AP)	215.5	187	0.075	211.3	187	0.108	233.5	187	0.012
Age + Cohort (AC)	195.4	175	0.139	192.2	175	0.177	193.9	175	0.156
Age + Period + Cohort (APC)	182.1	169	0.232	177.5	169	0.312	184.5	169	0.196
Model comparison**	**ΔDeviance**	**Δdf**	***p*-value[†]**	**ΔDeviance**	**Δdf**	***p*-value[†]**	**ΔDeviance**	**Δdf**	***p*-value[†]**
Drift effect : A nested in AD	410.7	1	<0.001	384.1	1	<0.001	408.5	1	<0.001
Period effect : A nested in AP	430.0	7	<0.001	403.9	7	<0.001	419.0	7	<0.001
Cohort effect : A nested in AC	450.0	19	<0.001	423.0	19	<0.001	458.6	19	<0.001
Period effect : AD nested in AP	19.3	6	0.004	19.8	6	0.003	10.6	6	0.103
Cohort effect : AD nested in AC	39.3	18	0.003	38.8	18	0.003	50.2	18	<0.001
Period effect : AC nested in APC	13.3	6	0.038	14.8	6	0.022	9.3	6	0.156
Cohort effect : AP nested in APC	33.4	18	0.015	33.8	18	0.013	48.9	18	<0.001

Abbreviations : df, degree of freedom;

*Deviance from Poisson model; [§]p-value from Goodness-of-fit test; [†]p-value from likelihood ratio test.

[**]Reference groups are: age group 40-44, period 1968-1972 and cohort 1941-1945. All models adjusted for gender.

[‡] The “drift” parameter represents a log-linear change in rate not exclusively identifiable as a period or cohort effect.

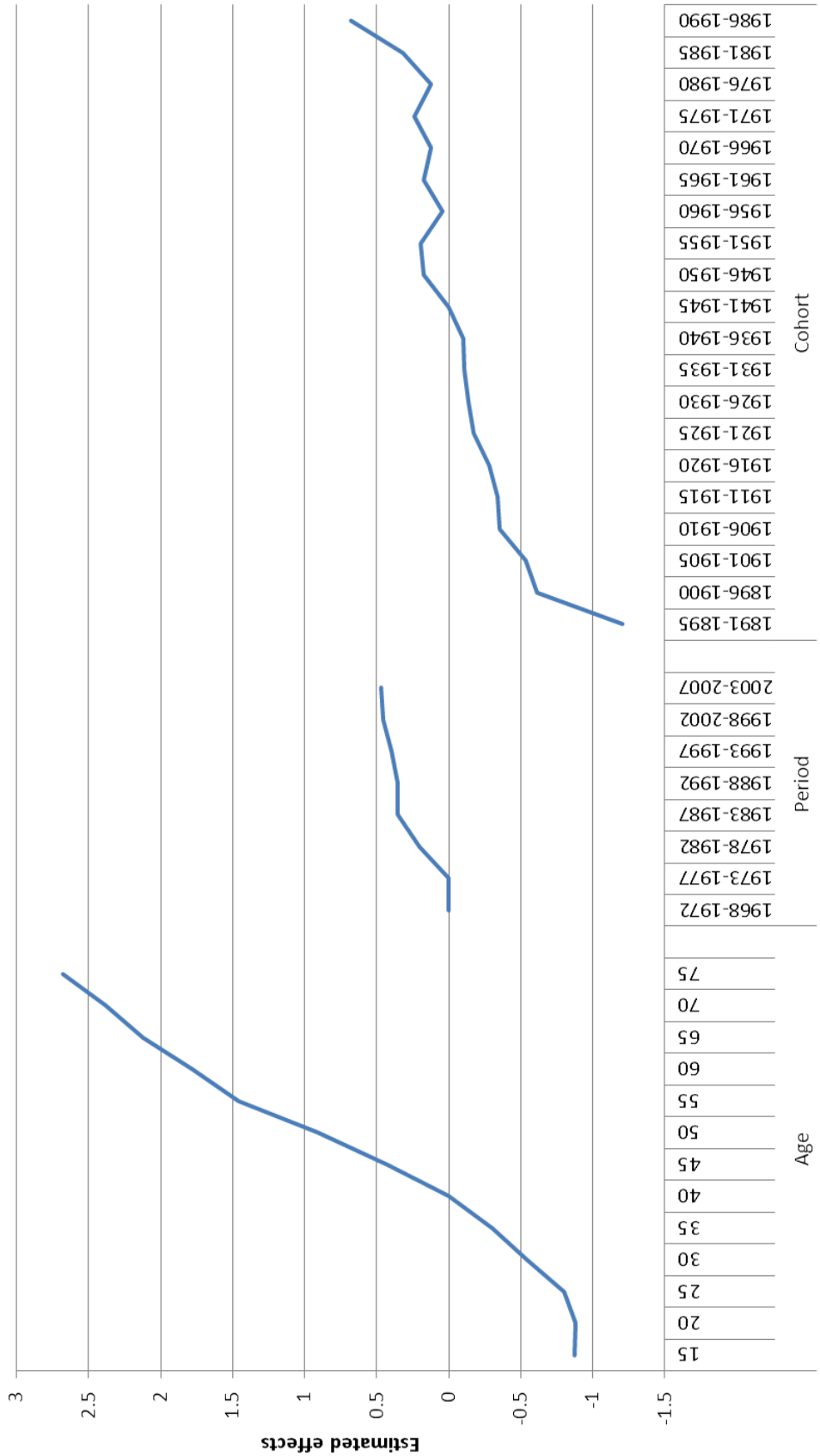


Figure 3.7 Estimated age, period and cohort effects on the incidence of NHL from the full APC linear model, Model 2

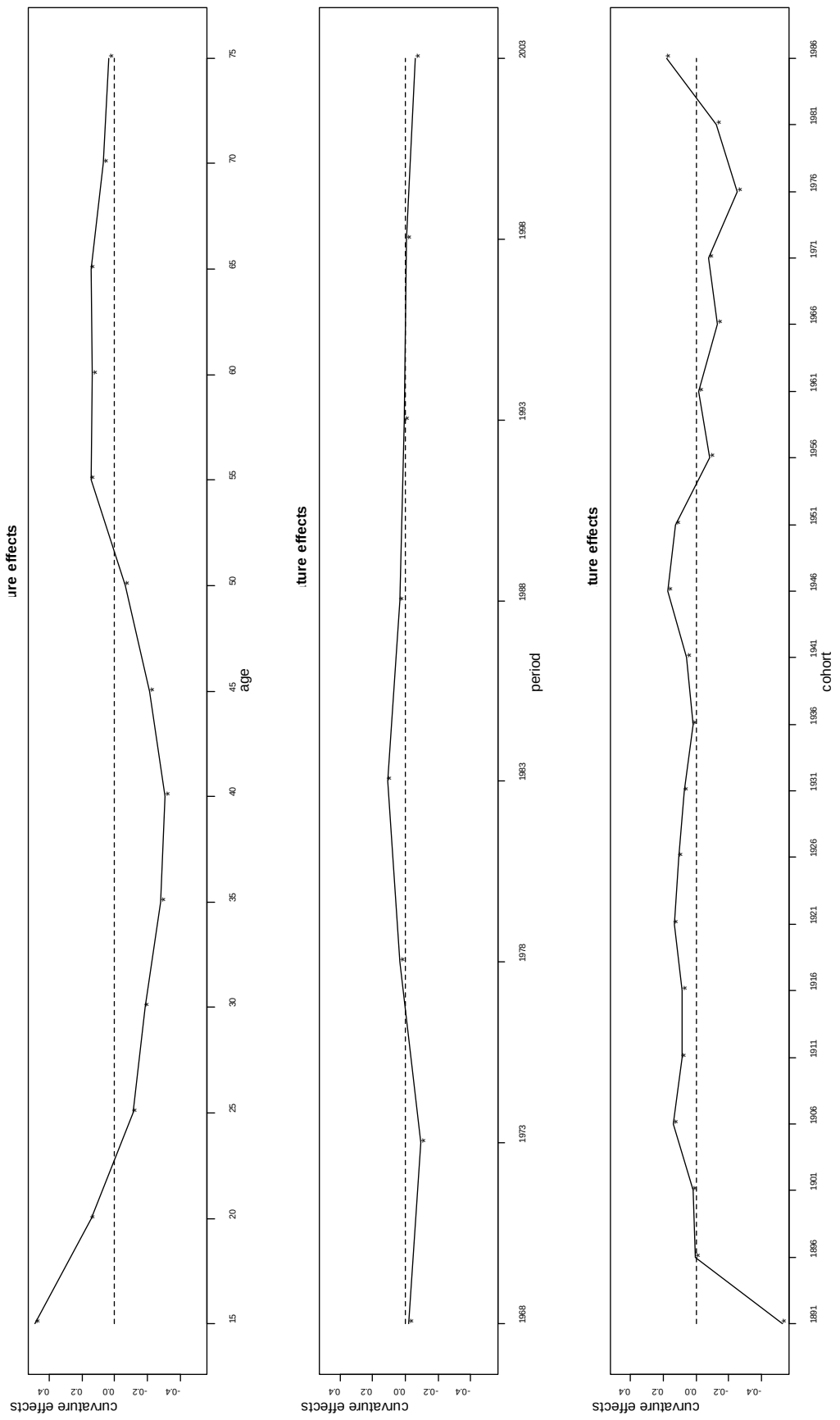


Figure 3.8 Curvature effects of a) age, b) period and c) cohort based on the full APC analysis of NHL adjusted for gender, 1968 – 2007.

3.5 Discussions

Our data showed the overall age-adjusted incidence rate of lymphoid neoplasms has increased markedly since 1968. Although many reasons have been suggested over the years, for example, changes in the classification of lymphoma, aetiology factors relating to virus/bacterial infections and environmental lifestyle changes, none of these has been able to explain the rise in rates satisfactorily. Our APC analysis on the incidence of NHL showed that all age, period and cohort effects may have contributed a significant impact in the development of NHL in the population for ages 15 to 79 years.

Trends of NHL and HL

As mentioned in **Chapter 1**, many countries investigated their lymphoma trends across time. Higher incidence rates of NHL was observed in North America, Australia and Europe than Asia (Ferlay *et al.* 2010). Most countries reported increasing trends of NHL in the past few decades, but in a few countries it started to level off in the 1990s (Sandin *et al.* 2006), while others (Bhurgri *et al.* 2005; Cartwright *et al.* 1999) including Singapore were still on the rise. HL is not as common as NHL, but the increasing trends were noted particularly among the adolescence. Hjalgrim *et al* (2008) reported the trends of HL in Singapore from 1968 to 2004, the incidence peak emerged among adolescents and young adults between the age 15 to 24 years, with a much faster rate observed in young females than males.

As explained in **Chapter 1**, diagnosis of lymphoma consisted of a series of investigations, including biopsy at site of presentation, full body imaging to confirm the degree of involvement in the whole body, plus bone marrow biopsy etc., and not just clinical presentation. As compared with other cancers, the chance of misdiagnosing as lymphoma is relatively low. There was no screening offer for lymphoma. Most of the lymphoma diagnosed in Singapore were aggressive subtypes, the disease presentation such as organ failure or palpable mass were fast, and it could be within weeks. The proportion of patients, who were rather well but incidental finding of slow growing lymphoma by body check-up, was not high. Lymphoma is a very heterogeneous group of cancer in the immune system, which consists of many entities with different levels of aggressiveness, targeting different age groups and may be caused by various risk factors. Cancer development is a multi-stage process. It started from initiation, promotion and progression stage. Different risk factors may affect different lymphoma subtypes at different stage of cancer development. It is almost impossible to identify a single risk factor, unless it is a common risk factor which affects the initiation of all subtypes of lymphoma.

Our results showed that the number of LN cases has increased 5 to 6 times in the last 40 years. The ASR of LN in 2003-2007 has doubled as compared in 1968. The increase is consistently observed in both males and females. The increasing trend, although at different pace across time, were consistent among the 4 major subtypes, namely HL, plasma cell neoplasms, lymphoid leukaemia and NHL. Since the beginning of cancer registry at 1968, several classifications have been proposed and implemented in the world: Rappaport, Kiel, Working Formulation, REAL, and WHO. We may not know the exact timing when pathologists in Singapore switched from one classification

system to another. The change in classification did not result in changing downward trend in specific subtypes corresponding to increase in trend in other subtypes. Thus the results suggested the increase in incidence rates of NHL observed was not a result of regrouping lymphoma within subtypes, but a genuine increase in the incidence in all lymphoma. As presented in **Appendix 1,** Hodgkin lymphoma, Non-Hodgkin lymphoma and Multiple Myeloma were traditionally considered as separate diseases, and Lymphoid Leukaemia were in the grey zone, bouncing between lymphoma and leukaemia depends on presentation and treatment regimen given.

APC models

In the last 20 years, several studies have attempted to examine the effects of time trends on the development of NHL using APC modelling. Holford *et al* (1992) using the Connecticut registry data from 1935-1989 showed increasing trends of NHL were attributed to both the period and cohort effects. Pollan *et al* (1998) reported that the rise in NHL in Spain between 1972 to 1997 was not only related to the period of diagnosis but also to the birth cohort. Liu *et al* (2003) studied 60,617 incident cases of NHL in Canada from 1970 to 1996, and suggested period effect played a major role, while birth cohort effect might be different according to gender. The tri-national assessment of 84,049 NHL incident cases from Sweden, Denmark and Finland between 1960 to 2003 concluded the predominance of calendar period over birth cohort effects (Sandin *et al.* 2006). The mixture of period and cohort effects were also supported in a study of nine population cancer registries by Bray *et al* (2001). However, the study by Viel *et al* (2010) on NHL incidence in the Doubs region in

France (1980-2005) supported a strong period effect only, starting from 1983 and stabilizing in 1992.

In our analysis, in order to overcome the identifiability problem, we assumed the first two periods are the same. This assumption was supported by our data that the age-standardized incidence rates were closest in the 1968-72 and 1973-77 (**Figure 3.2**). The classification of NHL subtypes as defined in Model 1 was based on the standard definition used in previous publications (Bray *et al.* 2001; Holford *et al.* 1992; Liu *et al.* 2003; Pollan *et al.* 1998; Sandin *et al.* 2006; Viel *et al.* 2010). Our results in the Model 1 supported both period and cohort effects as above mentioned studies.

Based on the updated WHO lymphoid neoplasm classifications, we re-defined NHL in Model 2 by including plasma cell myeloma cases, precursor lymphoma or indolent chronic lymphocytic leukaemia subtypes. The similarities between Models 1 and 2 in our results suggested that, the addition of other NHL subtypes did not alter the trends of the rest of NHL in Singapore, it decreased the p-value as the sample size increased by 1,577 cases (31% increase). It is possible these subtypes previously not considered as NHL as in Model 1, which also originated from B- or T-lymphocytes at different stage of differentiation, are behaving similarly as the rest of NHL subtypes and is considered in Model 2. In fact, small lymphocytic lymphoma (SLL) and chronic lymphocytic leukaemia (CLL) are considered as the same disease by WHO - “one disease at different stages, not two separate entities”. The surface markers in both are CD5+, CD19+, CD23+, weak CD79b and FMC7- by immunostaining. Traditionally SLL is considered as NHL, it usually presented in lymph nodes and referred to oncologist, while CLL is usually presented in blood stream and bone marrow,

and under the treatment of haematologist. The treatment regimen for CLL is similar to other indolent lymphoma (LRF 2010).

Age effect

As the age-specific rate of lymphoma was higher in older than younger adults, all studies agreed advancing age played a significant role in the development of lymphoma. Advancing age may be related to the duration of accumulation of certain exposures since birth, or the DNA repairing mechanisms are not as effective as younger age (Hoeijmakers 2009). The results of these two models confirmed that both period and cohort effects have contributed to the increasing trend of lymphoma in Singapore, on top of the age effect.

Period effect

As mentioned above, most of the lymphoma studies supported the effect of calendar period as one of the major contributing factor for the rise of lymphoma. The predominance of period effect suggests a change in a particular calendar year of diagnosis which affects all age groups. The changes in disease classification systems were frequently suggested as part of the reason for the rising trend. However, from the analysis of curvature effect based on the full APC in model 2, our result suggested minimal deviation from linear trends. We did not observe any sudden surge in the time when new classification proposed, or the few years after that; for example, the Kiel classification in 1974, the Working Formulation in 1982, the REAL classification

in 1994, the WHO classification in 2001. A change in method of diagnosis by using advancing imaging techniques, e.g. CT/MRI scan, full body PET scan, were also mentioned. Period effect may also be explained as a slow exposure to certain risk factors in the environment which affects all age groups simultaneously, e.g. low dose radiation exposure.

Cohort effect

The birth cohort effect suggests differences between distinct generations (birth cohorts) of individuals in the population. A change in lifestyle, a rapid exposure to an unknown risk factor which only affects certain age groups, or prevalence of an infectious disease over a lifetime could be the reasons. From the analysis of curvature effect in model 2, our result showed a sudden increase in deviation from linear trend among those who were born between 1941 and 1946, which coincide with the period of World War II in Singapore. It is reasonable to speculate their childhood during war period was affected by the environment and hence compromised the immune system in later development. The deviation from linear trend subsided from 1946 onwards. This might be due to improvement in the environment and public health after the war.

We have increasing evidence to show the importance of cohort effect in explaining the rising trend of lymphoma. In our case, 40 years is too short to have genetic mutations across generations, therefore environmental exposure would be the only possible reason. This may be reflected by the different causal environment factors that each successive birth cohort was exposed to as well as

societal change over time, which may have contributed to the increasing trend of lymphoma in Singapore.

There were many epidemiological studies in search for risk factors which may be associated with the development of lymphoma. Immunodeficiency is the strongest known risk factor, including primary immune deficiency, acquired/iatrogenic immune deficiency etc. For example, immunosuppression treatment received in solid organ transplant recipients, human deficiency virus (HIV) patients with depleted CD4+ T-lymphocytes leading to acquired immune deficiency syndrome (AIDS). NHL was considered as AIDS-defining cancers in 1987 by the Centre for Disease Control and Prevention (CDC) (CDC 1987). These subjects have higher risk of developing lymphoma, but they constitute few new cases in the general population. The theory was supported by studies in transplant and HIV cohorts (Grulich *et al.* 2007b; McGinnis *et al.* 2006; Shiels *et al.* 2009). From the Singapore HIV Observational Cohort Study (SHOCS), among the 1,504 patients infected with HIV who attended the Communicable Diseases Centre in 1985-2001, 834 patients developed one or more AIDS-defining conditions, with 8 new cases of Burkitt's lymphoma, 20 primary cerebral lymphoma and 25 extra cerebral NHL (Bellamy *et al.* 2004). HIV/Immunosuppression alone cannot explain for all the lymphoma incident cases that occurred in Singapore.

Model 3 LN

In our subsequent analysis on Model 3, when both NHL and HL was included, only age and cohort effect was detected, the period effect disappeared.

In all the previous studies, HL was considered as a separate entity, and were never analysed together with NHL trends. As mentioned in **Chapter 1**, the target age groups are slightly different in each subtype of lymphoma. Generally speaking, the NHL affects mainly adults and elderly, while HL affects early adolescents and older adults (i.e. 2 peaks in trends). As summarized in **Table 1.8**, the clinical presentation of HL and NHL are very different, e.g. nodal involvement and spreading, involvement of bone marrow and liver, and response to chemotherapy. However, the WHO classification system since 2001 grouped HL and NHL together under a new title, *Lymphoid Neoplasms*, and the concept of "Non-Hodgkin lymphoma" is no longer valid (Jaffe *et al.* 2001). Both the subtypes of HL and NHL are basically derived from lymphocytes, but only differ from various stage of cell maturation.

The new WHO classification system was the work and experience of more than hundred pathologists in the world, the classification system increases in complexity as the technology progress. For example, "*the B-cell neoplasm, cannot differentiate between DLBCL and classical Hodgkin lymphoma*" is one of the new entity in the updated WHO 2008 version (Jaffe 2009). Reed-Sternberg cells were once the gold standard for confirming Hodgkin lymphoma. The new entity tells us the possibility of misclassification between subtypes, especially between NHL and HL, in the past few decades. Therefore in the analysis of lymphoma trends in a country, it is unwise to consider HL and NHL separately.

When only NHL subtypes were considered in the APC model, the observed period effect might not be simply due to a change in classification, but a systematic error of misclassification between NHL and HL. The changes in

classification only increase the “branch” within subtypes, i.e. the increase in entities under an existing entity, rather than combine and pushing an existing subtype to another. On the other hand, if period effect was due to a slow exposure of environmental factors, it is possible the diverse group of lymphoid neoplasms cancelled out the individual effect.

The main purpose of this study is to clarify the lymphoma trends over the past few decades in Singapore, and in the attempt to figure out the possible answers. The important public health message from this APC analysis is, when the overall lymphoma trend was considered, we should use lymphoid neoplasms, including both HL and NHL subtypes, which will not be affected by internal misclassifications. As summarised in **Chapter 1**, the target age groups, clinical presentation, response to treatments, and potential risk factors are very different between HL and NHL. When it is aetiology-driven analysis, the HL and NHL subtypes should be considered separately. NHL should be further divided by aggressive and indolent natures if sample size is large enough to give enough power. There is a genuine increase in lymphoma incident over the years, and an increasing disease burden in the population especially in the elderly aged 50 and above.

3.6 Strengths and limitations of the APC analysis

Our data came from a very well-documented national cancer registry with a high coverage starting from the period 1968-1972, and maintaining coverage of close to 100% at all other periods. The incident cases were obtained not only from passive notification by medical practitioners, but actively acquired from hospital records, pathology reports and death certificates. The increase in cancer incidence observed is not due to artifactual reporting. Besides, a period of forty years (with 8 study periods) is long enough to detect any changes in trend.

This is the first study to use the WHO classification to compare the trend of lymphoid neoplasm, with traditional classifications used in previous published papers. This is particularly important since the WHO classification is now adopted universally, and in the latest 2008 version, the concept of "Non-Hodgkin lymphoma" is replaced by "B-cell neoplasms, T-/NK-cell neoplasms". In the dataset from National Cancer Registry, although several disease classification systems were implemented over the years, there were centralised all cases using only 2 coding systems, i.e. ICD-9 for the period of 1968 to 1992, and ICD-O for 1993 to 2007. Thus it reduces the chance of losing important information during the change in systems.

As compared with other cancers, lymphoma has been put through several complex classification systems and with numerous subtypes. We acknowledge that at the time of requesting data from Cancer Registry, we may have missed some very rare subtypes which were recently categorized as "Lymphoid Neoplasms" under the 2008 classification. These rare subtypes

usually have very few incidences, and thus should not have a significant impact on our total sample size and the subsequent APC analysis. The other limitation of our study is, even after including 40 years of data, the sample size of lymphoma cases is still small and hence lack the statistical power to further analyse by subtypes. It is important to understand the pattern of incidence rates which varies between the indolent and aggressive subtypes, in order to further investigate its relation between Asia and the Western countries.

Chapter 4

The Singapore Lymphoma Study

The Singapore Lymphoma Study (SLS) is a multi-ethnic case-control study of lymphoid neoplasms in Singapore. To our knowledge, this is the first epidemiologic study of malignant lymphomas conducted in a multi-ethnic Asian population in a tropical location. This study started in 2004, in an attempt to look at the potential risk factors of lymphoma which may be unique to a tropical country. The rest of epidemiological studies were conducted in the West where the environments were temperate.

4.1 Settings

The SLS is a hospital-based case-control study carried out in 3 major public hospitals (National University Hospital, Singapore General Hospital, Tan Tock Seng Hospital); and 2 national referral centres for skin diseases (National Skin Centre) and cancer (National Cancer Centre). The study was approved by the research ethics committees or Institutional Review Board (IRB) at each participating hospital or institution. The participants were recruited between April and October 2004 for the pilot phase, and between February 2005 and December 2008 for the main study. The commencement of recruitment in each institution depends on the IRB approval accordingly.

Written informed consent was obtained from all participants. This study comprised a standard questionnaire (see Appendix II) based interview by trained research nurses, the collection of 20ml peripheral blood or 2ml of saliva for genetic analysis, and pathology data from medical records. A face-to-face interview with both cases and controls was done by intensively-trained research staff in the respective hospital. Interviews were conducted in the language (English, Malay or Chinese dialect) which the participant was most familiar with, and were taped for quality control purposes with the consent of the interviewee.

Participants

The study base included Singapore citizens and permanent residents of Chinese, Malays and Indians origin aged 18 years and above.

Definition of cases: Eligible patients were newly diagnosed with malignant lymphoma within 6 months at the participating institutions, or the recently diagnosed subjects who received treatments for lymphoma at the participating hospitals. Histological diagnosis was confirmed by their panel of pathologists and haematologists. The classification was made according to the 2001 WHO classification system, including mature B- and T-cell neoplasms and Hodgkin lymphoma (ICD-O M9590-9596, M9650-9667, M9670-9699, M9700-9729, M9731-9734, M9823-9831 and M9940-9948). Relapsed cases after remission of first lymphoma diagnosis were not included. Lymphoma patients diagnosed with HIV infection or AIDS were not recruited since our university laboratory was not equipped with facilities to handle HIV virus samples.

Definition of controls: Controls were patients who were admitted to the departments of orthopaedic, internal medicine or general surgery in the same hospitals as the lymphoma patients. Only patients admitted for acute diagnosis during the same period were considered eligible. The current admission was not for any of the following diagnosis: asthma, atopic eczema or allergy, immune-related disorders, peptic ulcer disease, viral hepatitis or tuberculosis or suspicion of malignancy. Participants diagnosed with HIV infection or AIDS were not recruited. Controls were frequency-matched for age within 5 years age intervals, gender, study centres and month of diagnosis.

4.2 Data collection

The questionnaire used in the SLS was developed with reference, in part, to the questionnaire originally developed and used by the EpiLymph Group (Besson *et al.* 2006b), a project in European countries under the IARC in 2001-2003, and modified for local use. An in-person interview on the basis of the standardized questionnaire lasts about 50 minutes.

Basic demographics

Detailed information on personal demographics and other potential confounders were collected. SLS questionnaire included self-reported ethnicity and was categorized into Chinese, Malay and Indian for the analysis. Calendar age at recruitment (in years), gender (male, female), marital status (currently married, separated / divorce / widow, never married), country of birth (Singapore, Malaysia, China, Hong Kong, Taiwan, India, Others), education levels (in years),

current housing types (public housing ≤3 rooms, public housing >3 rooms, private housing including condominium or landed property, others), and family history of cancers (yes, no) were collected.

The body weight (in kg) and height (in cm) in usual adulthood were collected, and used to calculate the body mass index (BMI, in kg/m^2). The height was separated by gender, using the quartile cut-offs in each control group, and further grouped into quartiles in males (<164cm, 164-168.9cm, 169-172.9cm, ≥173cm) and females (<154cm, 154-157.9cm, 158-162.9cm, ≥163cm). Similar, the weight was grouped separately for males (<61kg, 61-68kg, 68.1-78kg, >78kg) and females (<54kg, 54-60kg, 60.1-70kg, >70kg).

General physical activity in the past one year in terms of hours spent on activities of (1) vigorous intensity (i.e. strenuous sports of tennis/swimming laps, loading or unloading trucks, shovelling or equivalent manual work), (2) moderate intensity (i.e. heavy housework, light sports including brisk walking/tai chi/bowling), (3) light intensity/sitting and (4) sleeping on weekdays and weekends were also recorded. Physical activity of different intensities were converted to metabolic equivalent levels (MET), defined as the ratio of work metabolic rate to standard resting metabolic rate (Ainsworth *et al.* 2000), in order to compute the total energy expenditure per week.

Dietary consumption was collected using a 64-item food frequency questionnaire (including 28 items on vegetables, 16 items on fruits, 14 items on meat with details in Appendix II), which was validated by the Singapore Chinese Health Study group (Hankin *et al.* 2001). Self-reported medical history such as Diabetes Mellitus (DM) and cataract were also collected as potential confounders.

4.3 Statistical analysis

Variables collected by the questionnaire were analysed by their status (cases or controls) using Chi-square test for categorical variables, or Student's *t*-test for continuous variables.

An unconditional logistic regression model was used to quantify the effect of individual variables on the risk of malignant lymphoma via the odds ratio (OR) estimate and its 95% confidence interval (CI). Crude OR and 95% CI were reported for the background variables excluding the matching variables that defined the controls and lymphoma cases.

Individuals with missing data for any variables were excluded for that analysis. All statistical tests were evaluated assuming a two-sided test at the 0.05 level of significance. Analyses were performed with STATA/SE 10.1 software. (StataCorp, Texas 77845 USA, 1984-2009)

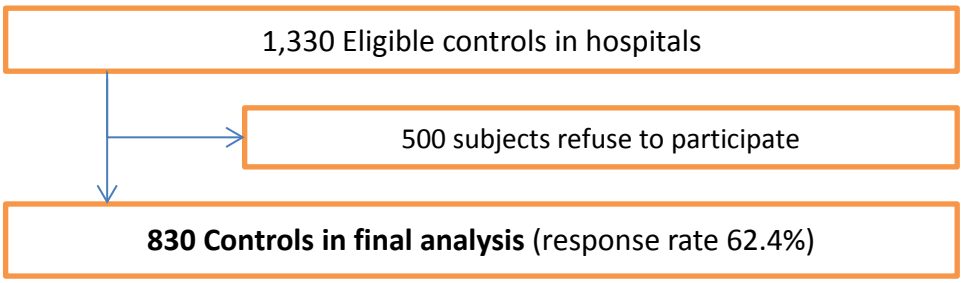
4.4 Response rate of the study

Of the 634 lymphoma cases ascertained during the 2004-2008 recruitment period, 31 subjects agreed to participate but passed away before the interview could be carried out. Furthermore, 59 eligible cases (9.8%) refused to participate or participation was declined by family members on his/her behalf, 3 cases (0.5%) refused to be interviewed and subsequently dropped out of the study. Thus this left us with 541 cases (315 males and 226 females) with a response rate of 89.7%. Among the 1330 controls ascertained and initially

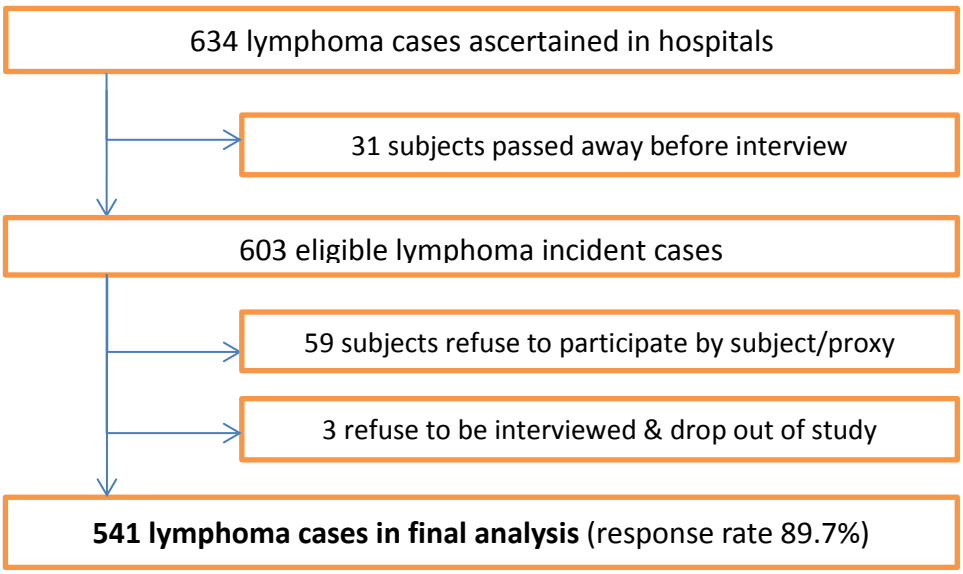
confirmed as eligible, 500 hospital patients (37.6%) refused to participate. There were thus 830 controls (response rate 62.4%) in this analysis (**Figure 4.1**).

Figure 4.1 Flowchart of SLS recruitment

a) Hospital controls



b) Lymphoma cases



4.5 Subtypes of lymphoma cases and hospital controls recruited

Table 4.1 shows the histological subtypes of lymphoid malignancy cases recruited in the SLS. There were 74 Hodgkin lymphoma (HL) (13.7%), 465 non-Hodgkin lymphoma (NHL) (86.0%) and 2 composite lymphomas (0.4%). NHL

consisted of 404 cases of B-cell and 61 cases of T-cell lymphoid neoplasms. Among the B-cell NHL, the aggressive diffuse large B-cell lymphoma (DLBCL) is the most common subtype (n=243), followed by the indolent follicular lymphoma (n=64) and marginal zone B-cell lymphoma (n=52).

Among the 541 lymphoma cases recruited, there were consistently more males than females in every lymphoma subtypes we recruited in this study. The male-to-female ratios ranged from 1.2:1 for DLBCL subtype, to 2.2:1 for T-/NK-cell neoplasms. The higher male to female ratios were concordant with previous Singapore Cancer Registry reports (NRDO 2010), and consistently observed across the world, as mentioned in **Chapter 1**.

In terms of ethnicity, 77.1% were Chinese, 16.5% and 6.5% from Malays and Indians respectively. The ethnic distributions were similar to the Singapore population (Statistics 2000), with higher proportions of Malays (16.5% vs. 13.9% in census) and less Indians (6.5% vs. 7.9% in census) recruited in our study. DLBCL subtype was the most prevalent subtype across 3 ethnic groups. Follicular lymphoma, NK/T-cell lymphomas and marginal zone B-cell lymphoma were more common in Chinese than the other ethnic groups. Hodgkin lymphoma was more frequent in Malays and Indians than Chinese. The 2 cases of composite lymphoma were recruited in Malays.

The hospital controls were mainly came from three departments, i.e. orthopaedic surgery, general medicine, and surgery, and the eligible controls were recruited from a wide range of admission diagnosis (**Table 4.2**), with none of the diagnosis comprise of more than 10% in total.

Table 4.1 Histological subtypes of lymphoid malignancies in the Singapore Lymphoma Study, 2004-2008.

Lymphoma subtype	All		Gender				Ethnicity					
			Male		Female		M:F ratio*	Chinese		Malay		Indian	
	No	(%)	*No*	(%)	*No*	(%)		*No*	(%)	*No*	(%)	*No*	(%)
Hodgkin lymphoma (HL)	74	(13.7)	46	(14.6)	28	(12.4)	1.6:1	42	(10.1)	20	(22.5)	12	(34.3)
Non-Hodgkin lymphoma (NHL)	465	(86.0)	267	(84.8)	198	(87.6)	1.3:1	375	(89.9)	67	(75.3)	23	(65.7)
B-cell neoplasms	404	(74.7)	225	(71.4)	179	(79.2)	1.3:1	320	(76.7)	64	(71.9)	20	(57.1)
• Diffuse large B-cell lymphoma	243	(44.9)	132	(41.9)	111	(49.1)	1.2:1	176	(42.2)	53	(59.6)	14	(40.0)
• Follicular lymphoma	64	(11.8)	39	(12.4)	25	(11.1)	1.6:1	58	(13.9)	3	(3.4)	3	(8.6)
• Marginal zone B-cell lymphoma	52	(9.6)	28	(8.9)	24	(10.6)	1.2:1	51	(12.2)	1	(1.1)	0	(0)
• Multiple myeloma	13	(2.4)	7	(2.2)	6	(2.7)	1.2:1	7	(1.7)	3	(3.4)	3	(8.6)
• Other B-cell types	32	(5.9)	19	(6.0)	13	(5.8)	1.5:1	28	(6.7)	4	(4.5)	0	(0)
T- *cell and NK-cell neoplasms*	61	(11.3)	42	(13.3)	19	(8.4)	2.2:1	55	(13.2)	3	(3.4)	3	(8.6)
Composite lymphoma (HL+NHL)	2	(0.4)	2	(0.6)	0	(0)		0	(0)	2	(2.3)	0	(0)
TOTAL	**541**	**(100)**	**315**	**(58.2)**	**226**	**(41.8)**	1.4:1	**417**	**(77.1)**	**89**	**(16.5)**	**35**	**(6.5)**

* Male-to-female ratio

Table 4.2 A list of admission diagnosis in hospital controls

Admission diagnosis	n	%	Admission diagnosis	n	%
Abscess	26	3.1	Orthopaedic - general	11	1.3
Accident - general	14	1.7	Orthopaedic - limb	72	8.7
Accident - fracture	81	9.8	Orthopaedic - spine	32	3.9
Anaemia	2	0.2	Pain - general	1	0.1
Appendicitis	36	4.3	Pain - abdominal	12	1.5
Arthritis	1	0.1	Pain - back	11	1.3
Bronchitis	4	0.5	Pain - chest	8	1.0
Cardiac problem	14	1.7	Pain - limb	7	0.8
Cellulitis	43	5.2	Pancreatitis	6	0.7
Cholecystitis	32	3.9	Pelvic inflammatory disease	5	0.6
DM and related problem	31	3.7	Pneumonia	8	1.0
Deep vein thrombosis	5	0.6	Prostate	1	0.1
Dengue	26	3.1	Psychiatric problem	2	0.2
Dental	1	0.1	Renal problem	9	1.1
Drug overdose	7	0.8	Respiratory problem	6	0.7
Epilepsy	2	0.2	Sepsis	6	0.7
Eye problem	5	0.6	Skin problem	10	1.2
Fever	16	1.9	Stroke	7	0.8
Gastrointestinal problem	48	5.8	Surgical problem	23	2.8
Gangrene	3	0.4	Syncope	3	0.4
Gout	3	0.4	Thyroid problem	4	0.5
Haemorrhoids	11	1.3	Ulcer	5	0.6
Headache	8	1.0	Uncontrolled hypertension	19	2.3
Hernia	9	1.1	Urinary problem	23	2.8
Ischemic heart disease	3	0.4	Vertigo	14	1.7
Infection	16	1.9	Wound-related problem	14	1.7
Jaundice	3	0.4	Others	19	2.3
Malaria	1	0.1			
Medical problem, assorted	40	4.8	**TOTAL**	**830**	**100**
Neurology	1	0.1			

4.6 Background characteristics of participants

The descriptive characteristics of the study population are presented in **Table 4.3**. The average age of cases and controls were 54.2 years (SD 16.0) and 50.3 years (SD 16.0) respectively, with 60% male participants. The ethnic difference among the cases was similar to the Singapore ethnic composition based on Census in year 2000 (Statistics 2000). However, we oversampled Malays (19.4%) and Indians (14.2%) in our control group.

In terms of birth place, we used the Singapore/Malaysia as one reference group, since Singapore and Malaysia were one country until Singapore's independence in 1965. A total of 74.1% of our subjects were born before the transition to independence. 10.1% of cases were born in other Asian countries as compared with 5.3% in controls (crude OR 2.01, 95%CI 1.33-3.03). Most of our participants immigrated to Singapore since childhood, and only 14 cases (2.6%) and 9 controls (1.1%) came after age of 20 years.

As compared with controls, a higher proportion of cases had either never received any formal education (11% in cases versus 9.3% in controls) or had ≥10 years of educations (32.8% versus 27.7%). 63% of the subjects were living in public housing with more than 3 bedrooms, and more cases were living in private condominium or landed property (12.9% vs. 4.9%; crude OR 3.91, 95%CI 2.51-6.09). The overall housing composition in this study population were similar to the types of dwelling in the Singapore household in the Census 2010 report (Statistics 2010).

While majority of subjects were currently married, 16.3% of cases and 24% of controls were never married (crude OR 0.59, 95%CI 0.45-0.79). A higher

percentage of cases than controls (48.2% versus 41.1%) reported being previously employed and could have resigned from current job due to diagnosis and treatment of lymphoma. Employment status will be further discussed in **Chapter 4**.

In terms of medical-related conditions, 34.4% of cases and 21.7% of controls presented with a family history of cancer in the first-degree relatives, and the crude risk of lymphoma was close to 2-fold. On the contrary, 24.8% of controls and 14.0% of cases presented with Diabetes Mellitus (crude OR 0.49, 95%CI 0.37-0.66). Both cases and controls consumed similar amount of fruits and vegetables by weight (p=0.649), which was calculated from our food frequency questionnaire. Only a subset of subjects (290 controls and 246 cases) was asked the additional question on medical history since Sept 2007, 25.5% controls and 16.3% cases were reported to have diagnosed with a history of cataract.

As analysed separately by gender, female hospital controls were on average taller (157.6cm, SD6.2) and heavier (63.3kg, SD14.1) than cases (155.7cm, SD7.1; 55.7kg, SD10.6); while the male controls were heavier (70kg, SD15.3 versus 67.7 kg, SD 13.0) but of about the same height (168cm, SD 8) as the cases. 24% of controls were in the highest weight quartile as compared with only 14.0% of cases (crude OR 0.46, 95%CI 0.32-0.65). In terms of BMI, 16.8% of controls and 7.0% of cases were considered obese (>30 kg/m^2). The mean usual adult BMI in the cases (23.6 kg/m^2, SD 4.1) was lower than the hospital controls (25.0 kg/m^2, SD 5.3) (crude OR 0.94, 95%CI 0.92-0.97). Both groups spent a similar amount of time on physical activities the year before, with an average of 20 minutes/day on vigorous intensity activities, <2 hours/day on moderate intensity activities, and less than 7 hours/day sleeping.

Table 4.3 Background characteristics of cases and controls in the Singapore Lymphoma Study, 2004-2008

Categories	Controls (n = 830)		Cases (n = 541)		*p*-value	Crude OR (95%CI)
	No	(%)	No	(%)		
Age (years)						
Range	18-87		18-90			
Mean age (SD)	50.3	(16.0)	54.2	(16.0)	<0.001	
Gender						
Male	495	(59.6)	315	(58.2)	0.603	
Female	335	(40.4)	226	(41.8)		
Ethnic group						
Chinese	551	(66.4)	417	(77.1)	<0.001	
Malay	161	(19.4)	89	(16.5)		
Indian	118	(14.2)	35	(6.5)		
Country of birth						
Singapore/Malaysia	786	(94.7)	482	(89.9)	0.001	1.00 (ref)
Other Asian countries[†]	44	(5.3)	54	(10.1)		2.01 (1.33-3.03)***
Education						
No formal education	77	(9.3)	59	(11.0)	0.092	1.00 (ref)
≤ 6 years	237	(28.6)	139	(25.9)		0.77 (0.51-1.14)
7-10 years	286	(34.5)	162	(30.2)		0.74 (0.50-1.09)
>10 years	230	(27.7)	176	(32.8)		1.00 (0.67-1.48)
Current housing type						
Public housing (≤3 rooms)	267	(32.2)	115	(21.5)	<0.001	1.00 (ref)
Public housing (>3 rooms)	511	(61.6)	347	(65.0)		1.58 (1.22-2.04)***
Condominium/Landed Property	41	(4.9)	69	(12.9)		3.91 (2.51-6.09)***
Others (e.g. nursing home)	11	(1.3)	3	(0.6)		0.63 (0.17-2.31)
Marital status						
Currently married	509	(61.3)	374	(69.9)	0.001	1.00 (ref)
Separated/widowed/divorced	122	(14.7)	74	(13.8)		0.83 (0.60-1.13)
Never married	199	(24.0)	87	(16.3)		0.59 (0.45-0.79)***
Employment status						
Currently employed	421	(50.8)	232	(43.4)	0.023	1.00 (ref)
Previously employed/Retired	341	(41.1)	258	(48.2)		1.37 (1.09-1.72)**
Never/Student/Housewife	67	(8.1)	45	(8.4)		1.22 (0.81-1.84)

Abbreviations: SD – standard deviation; * P-value<0.05, ** P-value<0.01, *** P-value<0.001.
[†] Other Asian countries including China/Hong Kong/Taiwan/Indonesia/Philippines/India/Pakistan etc.
Numbers did not add up to 830 controls and 541 cases due to missing data.

Table 4.3 (cont.)

Categories	Controls (n = 830) No	(%)	Cases (n = 541) No	(%)	*p*-value	Crude OR (95%CI)
History of cancer in the first-degree relatives						
No	644	(78.4)	337	(65.6)		1.00 (ref)
Yes	178	(21.7)	177	(34.4)	<0.001	1.90 (1.49-2.43)***
Diabetes Mellitus						
No	624	(75.2)	459	(86.0)		1.00 (ref)
Yes	206	(24.8)	75	(14.0)	<0.001	0.49 (0.37-0.66)***
Vegetables and fruit consumption (gram/year)						
Lowest quartile	207	(24.9)	133	(24.6)		1.00 (ref)
2nd quartile	208	(25.1)	152	(28.1)		1.14 (0.84-1.54)
3rd quartile	207	(24.9)	128	(23.7)	0.649	0.96 (0.71-1.31)
Highest quartile	208	(25.1)	128	(23.7)		0.96 (0.70-1.31)
Adult weight (kg)†						
Lightest quartile, gender-specific	235	(29.8)	190	(37.0)		0.97 (0.73-1.31)
2nd quartile, gender-specific	171	(21.7)	142	(27.6)		1.00 (ref)
3rd quartile, gender-specific	193	(24.5)	110	(21.4)	<0.001	0.69 (0.50-0.95)*
Heaviest quartile, gender-specific	189	(24.0)	72	(14.0)		0.46 (0.32-0.65)***
Mean weight, male (SD)	70.0	(15.3)	67.7	(13.0)	0.029	0.99 (0.98-1.00)*
female (SD)	63.3	(14.1)	55.7	(10.6)	<0.001	0.95 (0.93-0.97)***
Adult height (m)†						
Shortest quartile, gender-specific	188	(24.6)	144	(29.5)		1.12 (0.83-1.52)
2nd quartile, gender-specific	208	(27.2)	142	(29.1)		1.00 (ref)
3rd quartile, gender-specific	175	(22.9)	104	(21.3)	0.071	0.87 (0.63-1.20)
Tallest quartile, gender-specific	194	(25.4)	98	(20.1)		0.74 (0.54-1.02)
Mean height, male (SD)	168.3	(7.5)	167.8	(8.0)	0.362	0.99 (0.97-1.01)
female (SD)	157.6	(6.2)	155.7	(7.1)	0.002	0.96 (0.93-0.98)**
Adult body mass index, BMI (kg/m^2)						
Underweight (<18.5)	57	(7.5)	42	(8.7)		0.94 (0.61-1.44)
Normal (18.5-24.9)	368	(48.3)	289	(59.7)	<0.001	1.00 (ref)
Overweight (25.0-29.9)	209	(27.4)	119	(24.6)		0.73 (0.55-0.95)*
Obese (≥30)	128	(16.8)	34	(7.0)		0.34 (0.22-0.51)***
Mean physical activities in last year (hours/day)						
Vigorous activity (SD)	0.31	(0.9)	0.31	(0.9)	0.847	1.01 (0.89-1.15)
Moderate activity (SD)	1.67	(2.2)	1.48	(2.2)	0.120	0.96 (0.91-1.01)
Light activity / Sitting (SD)	15.27	(2.8)	15.24	(2.8)	0.843	1.00 (0.96-1.04)
Sleeping (SD)	6.74	(1.6)	6.98	(1.7)	0.009	1.09 (1.03-1.17)**
Mean MET/week‡ (SD)	264.6	(51.7)	260.9	(52.7)	0.205	1.00 (1.00-1.00)

Abbreviations: SD – standard deviation; * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

† Adult height and weight were summarised by gender, and grouped into quartiles based on control distributions.

‡ Physical activity expressed in metabolic equivalent intensity level, MET/week.

Numbers did not add up to 830 controls and 541 cases due to missing data.

4.7 Strengths and limitations of hospital based case-control study

This is the first multi-ethnic hospital-based case-control study in Asia. In order to understand the high lymphoma rate in Singapore as compared with the rest of the Asian countries, an effort has made to find out the aetiology background.

Although lymphoma is the top 10 common cancers in Singapore, the number of cases occurring each year is scanty. Based on the Singapore Cancer Registry report, there were about 450 incidences each year, including non-residence in Singapore, between 2003 and 2007(NRDO 2010). In order to investigate rare cancer such as lymphoma, due to the long waiting time for cases to accumulate, the retrospective design of case-control study would be able to investigate the various aetiology factors of this rare disease, with relatively shorter time and less resource than a cohort study.

Strengths of study

The Singapore Lymphoma Study was first launched in 2004 as a pilot study, to access logistics and gather information for the subsequent large-scale main study in 2005 to 2008. We have tested on the possibility of recruiting controls from both hospitals and general population. However, due to the stringent matching criteria, we were forced to abandon the population control due to poor response rate, i.e. one successful neighbourhood control in 42 households approached. This small scale preliminary study conducted in order to validate the study in the hospital setting, check the feasibility of recruitment in

clinics and hospital wards, and finalize the standard operating procedures for the main study.

The multi-centre design, including 2 national referral centres for cancer and skin diseases, covered the majority of public facilities in Singapore. The high coverage of study centres provided an access to a representative sample of eligible incident cases in this country.

The data were collected using standardized techniques. In order to maintain comparability with previous studies conducted in other populations, the questionnaire used in the Singapore Lymphoma Study was already validated by the EpiLymph group (Besson *et al.* 2006b), a project in European countries under the IARC in 2001-2003. The questionnaire also provides a wide coverage on lifestyle factors, medical history and occupational backgrounds. The Asian diet questionnaire is uniquely designed for the Singapore context by a cohort study group, the Singapore Chinese Health Study. The diet questionnaire has already been validated in 2001 and published in many international peer-reviewed journals.

Limitations of study

At the same time, we are mindful of the limitations that are inherent in the retrospective nature of this study. We aware that the controls recruited from the hospital-based study design might have **Berkson's bias**, where the exposure of interest increases the chance of hospital admission, thus leading to a higher exposure rate among hospital controls than normal population in the study base.

We have several measures to eliminate the selection bias by: (1) hospital controls were recruited based on admission diagnosis, instead of their exposure of interest. (2) Inclusion and exclusion criteria were set up in advance to screen out patients whose admission diagnosis might have higher exposures than normal populations, but not excluded people with a history of such diagnosis. Patients admitted for asthma, atopic eczema/allergy, immune-related disorders which have been suggested as potential risk factors for the development of lymphoma in the literature would not be recruited (Alexander *et al.* 2007).

Besides, these hospitals are generalized hospitals with multidisciplinary divisions. No matter what disease they developed, these patients would go through the same referral pattern from primary physicians to the hospitals, and likely they came from the nearby geographic location of their residence. Therefore, recruiting controls from the same hospital where lymphoma patients were recruited, it ensured that the controls were from the same catchment population where the cases were generated. The hospital controls were also time-matched with cases whenever there was a new case recruited into the study, thus to ensure the controls were came from a similar but dynamic study base which give rise to the case.

The relatively low participation rate (62.4%) in our hospital controls might also introduce a **selection bias**. We did not have the information of the non-responders, so we could not compare the difference between non-responders and participants in our study, in terms of education or lifestyle backgrounds.

Only hospital controls with acute diagnosis at admission were recruited so as to avoid the recruitment of patient with long term medical problems with long stay in hospital, whose exposure might be different from the general populations. We have also made an effort to ensure that none of the diagnosis exceeded 10% of the total controls recruited, in order to avoid recruiting hospital patients with exposure to certain risk factors that we have no knowledge at the time of recruitment. We did not recruit hospital controls based on the potential risk factors in their medical history in order to avoid high prevalence of these conditions which may shift the OR towards the null. We hope through these procedures we would minimize the confounding factors which we may not be able to control for.

Both cases and controls were recruited and interviewed by research staff, therefore we could not blind the research staff with regards to the disease state and this might introduce **interviewer bias**. We had trained our staff intensively on interview techniques using standardized questionnaires, following the standard operating procedures to conduct interviews. All interviewers were required to interview both cases and controls, and the questionnaire was administrated the same way to all participants regardless of their status. The interviews were voice-recorded for quality control purpose throughout the recruitment period; the recordings were constantly monitored to make sure the interviews were consistent over time.

We chose hospitalized patients as controls instead of fully healthy subjects with no medical history. When both cases and controls had gone through similar experience in hospital, both were pre-occupied by their sickness under the same environment, we believe they will recall previous exposures

similarly. Since most of the general population did not understand lymphoma and the reasons behind the development of lymphoma, any difference reported between cases and controls might be non-differential.

Our criteria for matching of controls with cases rely on a combinations of strong confounding factors, e.g. age ± 5 years, gender, hospital, and month of recruitment. When the project first started, controls were individually matched with cases, and matched on ethnicity as well. However during the early phase of study, we noticed we had a hard time of getting suitable candidates in hospital since the combination limits the size of the available pool. As a trade-off for response rate and recruitment duration, we therefore used frequency matching on existing criteria, and adjusted for ethnicity in the analysis phase, in attempt to control for any other confounding factors related to ethnicity that we did not manage to control for during recruitment.

As compared to a national registry, the number of lymphoma cases in this study was much smaller, thus limiting our analysis of aetiology factors by rare subtypes. We acknowledged that we did not manage to interview some of the lymphoma patients before they passed away. This could reflect a loss of information in the severely aggressive cases of lymphoma, whose lifestyle factors and occupational exposure might be different from the rest of indolent or less aggressive subtypes.

Chapter 5

Association between occupational history and the risk of lymphoma

Although the risk factors for lymphoma include inherited and acquired immunodeficiency conditions, infectious, physical and chemical agents have also been reported (Alexander *et al.* 2007). At present, no conclusive evidence of causal relation between occupation and increased lymphoma risk exists. Most of the literature reported inconsistent results which may be due to a lack of specific individual-level exposure information. In a recent review on occupation and risk of NHL, Boffetta and de Vocht (2007) reported a significant increase in the risk of lymphoma among workers in the printing industry, wood workers, farmers (especially in animal husbandry) and teachers. Among all occupations, the most notable finding reported from previous studies is the observed association between teaching profession and the risk of NHL (Alexander *et al.* 2007).

5.1 Literature review on occupational history and the risk of lymphoma

Teaching profession

Numerous studies have examined the relation between the teaching profession and the risk of NHL, and these are summarized in **Table 5.1**. Findings from a meta-analysis of 19 studies showed an elevated risk of NHL

among teachers (RR 1.47, 95%CI 1.34-1.61) (Boffetta & de Vocht 2007). However, it has been suggested that the positive association between the teaching profession and NHL could be due to publication bias (Baker *et al.* 1999). Difference in gender effect have been reported in Italian case control studies where female teachers (OR 1.7, 95%CI 1.0-2.7) appeared to have a higher risk of developing NHL than male teachers (OR 0.7, 95%CI 0.3-1.3) (Costantini *et al.* 2001; Miligi *et al.* 1999). No evidence of difference was observed in any specific teaching profession in a Swedish cohort study, that is, whether the subjects were primary or secondary school teachers, arts or theoretical subjects teachers, principals or headmasters (Cano & Pollan 2001). There has been no report on the association between teaching profession and HL in the past twenty years, this could be due to the small sample size of HL in most studies.

Reports on the association between NHL and occupation including teaching profession are mostly from the Western populations. Could the increase in NHL in Singapore be contributed by the changes in the working pattern from a trading port in the 50's and 60's to rapid industrialization in the 70's and beyond? The aim of this study is to examine the possible association between occupations in Singapore based on the Singapore Standard Occupation Classification and the risk of lymphoma based on information collected from participants of the Singapore Lymphoma Study.

Other occupations

The diverse of occupational exposure and in respective industry formed a diverse matrix of exposure. Very few people worked in a single environment throughout the entire occupational history. Without any *a priori* knowledge on

the latency period from exposure to the initiation of lymphoma, thus it increase the difficulty in analysing the association between occupational exposure and risk of lymphoma, unless the specific agent exposed to is discrete and easy to measure.

Pesticide exposure is one of the most studied risk factor in lymphoma. Alexander *et al.*, (2007) published a very detail review on the association of occupational and residential exposure to pesticides and risk of NHL in cohort and case-control studies. Pesticides comprise a long list of chemicals, e.g. insecticide, herbicide, DDT, phenoxy acids, organophosphates, triazines, and carbamates etc. These include studies on those with frequent contract with pesticides including farmers, pesticide manufacturers, pesticide applicators, chemical production workers, and even military veterans who served in Vietnam. However, these studies have reported inconsistent results.

Apart from pesticides, farmers in animal husbandry may also exposed to oncogenic viruses carried by farm animals. Workers in slaughter house and meat inspectors have been found elevated risk of NHL than other occupations (Pearce & McLean 2005). Exposure to chemicals showed inconsistent results, partly due to the difficulty in measuring correct exposure levels, and the problem of multiple exposure to different chemicals etc (Lamm *et al.* 2005). Studies Organic solvents showed in suggested to be involved in the development of NHL (Rego 1998), but review studies suggested asbestos (Seidler *et al.* 2010; Weisenburger & Chiu 2002) , gasoline (Kane & Newton 2010b), benzene (Bezabeh *et al.* 1996; Kane & Newton 2010a) does not increase risk of NHL.

Alexander *et al.* (2007) summarised evaluation of epidemiological studies of occupations yielded no specific exposure that is consistently

associated with NHL. Studies on non-ionizing UV radiation from sunlight may played reduce the risk of developing in NHL, while studies on other ionization radiation found no significant associations. Cano and Pollan (2001) reported a cohort study of close to 3 million Swedish men and women, and 7610 NHL cases ascertained at the end of 19 years of follow up. Many occupations reported with relative risk more than 1.20, including accountants and auditors, secretaries and typists, auctionists, non-specific rail and road transport workers, telecommunications traffic officers, telegraph and radio operators, photographic-laboratory workers and other production and related work in men and metal platers and coaters, truck and conveyor operators and store and warehouse workers in women. No specific agents were identified in most of the occupations.

Table 5.1 Studies on NHL risk among teachers since 1999

Reference	Country (study)	Period	Study design	Occupation	Subtype	Risk estimates	(95% CI)
Baker *et al.* (1999)	-	1950-1990	Meta-analysis of 13 studies	Teacher	NHL	1.36	(1.13-1.62)
Miligi *et al.* (1999)	Italy (12 areas)	1991-1993	Case-control	Teacher (women only)	NHL	1.70	(1.00-2.70)
Cano & Pollan (2001)	Sweden	1971-1989	Cohort	Principal, headmaster	NHL	1.22	(0.76-1.97)
				Teacher, theoretical subjects	NHL	1.21	(0.91-1.62)
				Teacher, arts	NHL	1.44	(0.95-2.19)
Constantini *et al.* (2001)	Italy (12 areas)	1991-1993	Case-control	Teacher (men only)	NHL	0.70	(0.30-1.30)
Zheng *et al.* (2002)	USA (Kansas, Nebraska)	1979-1986	Case-control	Teacher (men only)	NHL	2.50	(1.00-6.50)
Svec *et al*. (2005)	USA (24 states)	1984-1998	Case-control	Teacher	NHL	1.15	(1.10-1.20)
					HL	1.41	(1.20-1.66)
					MM	1.21	(1.13-1.29)
Ji & Hemminki (2006)	Sweden (Swedish Family Cancer Database)	1958-2002	Ecological (Cancer registry)	Teacher (men only)	NHL	1.10	(1.00-1.20)
Boffetta & de Vocht (2007)	-	1950-1998	Meta-analysis of 19 studies	Teacher	NHL	1.47	(1.34-1.61)

5.2 Occupation history in the Singapore Lymphoma Study

A detailed description of the Singapore Lymphoma study has been provided in **Chapter 4**. In brief, the Singapore Lymphoma Study is a hospital-based case-control study conducted in Singapore from 2004 to 2008. Lymphoma patients and hospital participants were interviewed using structured standardized questionnaire by trained research staff. Apart from basic demographics and potential confounders, we elicited a complete occupational history which included all jobs lasting over one year since graduation from school. For every job, information collected included the year in which employment began and ended, occupational title and industry, a description of job duty and ever use of chemicals or operation of machinery.

The Singapore Standard Occupational Classification (SSOC) (2006) was used for coding the occupation for all subjects; with selected entities of occupations presented in **Table 5.2**. The SSOC adopts the basic framework and principles of the International Standard Classification of Occupations 1988 (ISCO-88). It is reviewed and updated periodically to reflect changes in the employment structure and the emergence of new occupations in Singapore. The SSOC comprises 5-digit codes with each digit giving increasing specificity regarding the individual occupation: The 1-digit code represents a very broad field of work, and the subsequent digits codes provide a more specific description. For example:

- 2 - Professional
- 23 - Teaching Professionals
- 231 – University, Polytechnic and Other Higher Education Teachers
- 2310 – University, polytechnic and other higher education teachers
- 23101 – University lecturer

Table 5.2 Selected 1- and 2-digit codes from the Singapore Standard Occupational Classification 2005 (Statistics 2006)

Coding	Occupation
1	**Legislators, Senior Officials and Managers**
11	Legislators and senior officials
12	Corporate managers
13	Working proprietors
2	**Professionals**
21	Physical, mathematical and engineering science professionals
22	Life science and health professionals
23	Teaching professionals
24	Business professionals
25	Legal professionals
29	Professionals not elsewhere classified
3	**Associate Professionals and Technicians**
31	Physical and engineering science associate professionals
32	Life science and health associate professionals
33	Teaching associate professionals
34	Finance, sales and related business associate professionals
39	Associate professionals not elsewhere classified
4	**Clerical Workers**
41	Office clerks
42	Customer service clerks
49	Clerical workers not elsewhere classified
5	**Service Workers and Shop and Market Sales Workers**
51	Service workers
52	Shop and market sales workers
6	**Agricultural and Fishery Workers**
61	Agricultural workers
62	Fishery workers
7	**Production Craftsmen and Related Workers**
71	Building trades workers
72	Metal, machinery and related trades workers
73	Precision, handicraft, printing and related trades workers
74	Food processing, woodworking, textile, leather and related trades workers
79	Production craftsmen and related workers not elsewhere classified
8	**Plant and Machine Operators and Assemblers**
81	Stationary plant and related operators
82	Machine operators and assemblers
83	Drivers and mobile machinery operators
9	**Cleaners, Labourers and Related Workers**
91	Cleaners and related workers
92	Porters, attendants and related workers
93	Labourers and related workers
X	**Workers Not Classifiable By Occupation**

For this study, since there is no prior knowledge on the association of duration of exposure in occupation to the onset of disease, we analysed the association of occupation history with lymphoma using the following 3 methods:

1. The first occupation : it was the first job that the subject took up after leaving school, or his/her first employed job if he or she had not attended school which lasted more than one year.

2. The longest occupation : this was determined for each subject using the longest duration of any occupation reported.
    - If the subject took up the same job on more than one occasion, the total duration in years would be added up together;
    - If two or more occupations lasted for equal period of time, it would be removed from the analysis of longest occupation since we cannot determine which was the longest.

3. Ever in occupational history : they were counted in as long as the subject has ever been employed in that particular occupation for at least a year.
    - We have collected up to 7 different occupations, which mean the subjects could be enlisted in a maximum of 7 different occupations, which were not mutually exclusive.

5.3 Statistical analysis

The distribution of occupations using 1-digit SSOC code among the lymphoma cases and controls were compared by simple chi-square test, with the occupation of interest verses the rest of occupations in the first and the longest occupation. We further analysed the 2-digit SSOC codes of selected occupations which the subjects had ever been employed in the entire occupational history by chi-square test.

As mentioned in **Chapter 4**, an unconditional logistic model was used to quantify the association between occupations of interest and the risk of lymphoma. All analyses were adjusted for potential confounders including age (as a continuous variable), gender (male/female), ethnic group (Chinese/Malay/Indian), education level (no formal education / ≤6 years / 7-10 years / >10 years), current housing type (public housing ≤3 rooms / public housing >3 rooms / private housing / others) as a surrogate for socio-economic status, and history of any cancer in a first degree relative (yes/no). In addition, other potential confounders (e.g. BMI, country of birth) which did not change the risk estimates of the exposure of interest by over 10% were not considered for inclusion in the final models.

5.4 Results

Among the 1,371 participants (830 controls and 541 lymphoid neoplasms cases), 99.5% of participants (n=1,364) provided information on their current employment status. 653 (47.9%) were currently under employment, 599 (43.9%) retired from occupation, and 112 (8.2%) had never worked (e.g. homemaker or students etc). 1,236 participants disclosed detailed occupations which lasted for at least 1 year; whereas another 23 participants (14 controls and 9 LN cases) who did not disclose any occupation history were treated as missing data. The current analysis was focused on 749 controls (456 males and 293 females) and 487 LN cases (295 males and 192 females) who provided detailed occupational history. For each subject, a maximum of 7 different job descriptions in the entire working history was provided.

In **Table 5.3**, using the 1-digit code of the SSOC to screen both the first and longest held occupation, there was a significantly higher percentage of "Professionals" (group 2) who were LN cases (first occupation: 9.7%; longest occupation: 8.6%) as compared to the controls (4.4%; 5.1%), respectively. This was consistently observed in NHL and HL subtypes in both the first and longest occupation. On the other hand, lower percentages of LN cases were observed in "Plant and machine operators and assemblers" (group 8) for first occupation (cases=14.4%; controls=19.0%); and "Cleaners, labourers and related workers" (group 9) for the longest held occupation (11.9%; 15.9%). We did not observe any association in other occupations such as clerical workers or craftsman.

Table 5.3 Distribution of the first and longest held occupation among the lymphoid neoplasms cases and controls in the Singapore Lymphoma Study.

Singapore Standard Occupational Classification		Controls		Lymphoid neoplasms			Non-Hodgkin lymphoma			Hodgkin lymphoma		
		No	(%)	*No*	(%)	*p*-value[‡]	*No*	(%)	*p*-value[‡]	*No*	(%)	*p*-value[‡]
Group	***First Occupation***											
1	Legislators, Senior Officials and Managers	27	(3.6)	24	(4.9)	0.253	20	(4.7)	0.368	4	(6.9)	0.209
2	**Professionals**	33	(4.4)	**47**	**(9.7)**	**<0.001**	**40**	**(9.4)**	**0.001**	**7**	**(12.1)**	**0.010**
3	Associate Professionals and Technicians	61	(8.1)	47	(9.7)	0.359	39	(9.1)	0.567	8	(13.8)	0.138
4	Clerical workers	86	(11.5)	64	(13.1)	0.383	57	(13.3)	0.354	7	(12.1)	0.893
5	Service Workers and shop and market sales	132	(17.6)	72	(44.8)	0.189	64	(15.0)	0.237	8	(13.8)	0.458
6	Agricultural and Fisher Workers	21	(2.8)	17	(3.5)	0.494	17	(4.0)	0.275	0	(0)	0.196
7	Production craftsmen and related workers	96	(12.8)	61	(12.5)	0.880	53	(12.4)	0.829	8	(13.8)	0.831
8	**Plant and Machine Operators and Assemblers**	142	(19.0)	**70**	**(14.4)**	**0.037**	62	(14.5)	0.051	8	(13.8)	0.330
9	**Cleaners, Labourers and Related Workers**	137	(18.3)	74	(15.2)	0.157	69	(16.1)	0.346	**4**	**(6.9)**	**0.028**
X	**Workers Not Classifiable By Occupation**	14	(1.9)	11	(2.3)	0.635	7	(1.6)	0.771	**4**	**(6.9)**	**0.012**
	Total number of first occupations	**749**		**487**			**428**			**58**		
Group	***Longest Occupation***											
1	Legislators, Senior Officials and Managers	45	(6.0)	39	(8.0)	0.176	33	(7.7)	0.264	6	(10.3)	0.193
2	**Professionals**	38	(5.1)	**42**	**(8.6)**	**0.014**	**35**	**(8.2)**	**0.035**	**7**	**(12.1)**	**0.026**
3	Associate Professionals and Technicians	85	(11.4)	61	(12.5)	0.542	52	(12.2)	0.692	9	(15.5)	0.344
4	Clerical workers	90	(12.1)	57	(11.7)	0.855	52	(12.2)	0.959	5	(8.6)	0.436
5	Service Workers and shop and market sales	139	(18.6)	72	(14.8)	0.081	62	(14.5)	0.071	10	(17.2)	0.796
6	Agricultural and Fisher Workers	10	(1.3)	7	(1.4)	0.884	7	(1.6)	0.682	0	(0)	0.375
7	Production craftsmen and related workers	80	(10.7)	54	(11.1)	0.834	50	(11.7)	0.609	4	(6.9)	0.360
8	Plant and Machine Operators and Assemblers	129	(17.3)	87	(17.9)	0.788	77	(18.0)	0.754	9	(15.5)	0.733
9	**Cleaners, Labourers and Related Workers**	119	(15.9)	**58**	**(11.9)**	**0.049**	55	(12.9)	0.153	**3**	**(5.2)**	**0.028**
X	**Workers Not Classifiable By Occupation**	12	(1.6)	10	(2.1)	0.562	5	(1.2)	0.545	**5**	**(8.6)**	**<0.001**
	Total number of longest occupations[†]	**747**		**487**			**428**			**58**		

[†] 2 subjects with equal duration of occupations were excluded in the longest occupation.

[‡] *p*-value from chi-square test of significance between group of interest versus others.

Following the results of the first and longest held occupations based on 1-digit SSOC codes, we analysed selected occupational groups for the association with lymphoid neoplasms using 2-digit SSOC codes. These included those who had ever worked as a “Professional”, “Plant and Machine Operators and Assemblers”, and “Cleaners, Labourers and Related Workers”. However “Workers Not Classifiable by Occupation” including those working odd jobs which could not be identified and grouped according to job title or nature, were not further analysed since we did not have enough information about it. The “Professional” (group 2) and “Associate Professional” (group 3) are occupations similar in terms of exposures, but different in ranking of job title, as such we included the latter group into consideration for the subsequent analysis. As shown in **Table 5.4**, a higher proportion of LN cases were employed as Teaching professionals (code 23) and Business professionals (code 24) as compared with controls. A significantly lower proportion of LN cases were employed as machine operators and assemblers (code 82) ($p=0.046$), and labourers and related workers (code 93) ($p=0.009$).

Table 5.4 Selected occupations of those who had ever been employed as in the entire occupational history.

1 digit code	2 digits code	Occupation *	Controls n (%)	LN Cases n (%)	*p*-value ‡
2		**PROFESSIONALS**			
	21	Physical, Mathematical and Engineering Science Professionals	29 (3.9)	24 (4.9)	0.370
	22	Life Science and Health Professionals	0 (0)	2 (0.4)	0.079
	23	**Teaching Professionals**	**12 (1.6)**	**23 (4.7)**	**0.001**
	24	**Business Professionals**	**7 (0.9)**	**17 (3.5)**	**0.001**
	25	Legal Professionals	1 (0.1)	1 (0.2)	0.759
	29	Professionals Not Elsewhere Classified	6 (0.8)	10 (2.1)	0.057
3		**ASSOCIATE PROFESSIONALS AND TECHNICIANS**			
	31	Physical and Engineering Science Associate Professionals	55 (7.3)	29 (6.0)	0.343
	32	Life Science and Health Associate Professionals	15 (2.0)	14 (2.9)	0.322
	33	Teaching Associate Professionals	14 (1.9)	12 (2.5)	0.476
	34	Finance, Sales and related Business Associate Professionals	36 (4.8)	26 (5.3)	0.675
	39	Associate Professionals Not Elsewhere Classified	0 (0)	0 (0)	
	23,33†	Teaching (Professions + Associate Professions)	**25 (3.3)**	**34 (7.0)**	**0.003**
	24,34†	Business (Professions + Associate Professions)	41 (5.5)	38 (7.8)	0.102
8		**PLANT AND MACHINE OPERATORS AND ASSEMBLERS**			
	81	Stationary Plant and Related Operators	12 (1.6)	9 (1.9)	0.744
	82	**Machine Operators and Assemblers**	**154 (20.6)**	**78 (16.0)**	**0.046**
	83	Drivers and Mobile Machinery Operators	101 (13.5)	69 (14.2)	0.733
9		**CLEANERS, LABOURERS AND RELATED WORKERS**			
	91	Cleaners and Related Workers	128 (17.1)	78 (16.0)	0.621
	92	Porters, Attendants and Related Workers	44 (5.9)	23 (4.7)	0.382
	93	**Labourers and Related Workers**	**101 (13.5)**	**42 (8.6)**	**0.009**

* Participants could be presented in more than one occupation.

† including subjects who were employed in both groups of occupation.

‡ *p*-value from chi-square test of significant between group of interest versus all other occupations.

When teaching and associate teaching professions were considered together (i.e. code 23 and 33), there were 34 LN cases (7.0%) and 25 controls (3.3%) who reported being in 'teaching profession' in the entire occupational history (p=0.003). These included 10 primary school teachers (code 23300), 13 teachers in secondary school and above (code 23102 & 23201), 13 private tutors (code 33910) and 23 other different types of teaching professions (**Table 5.5**). However, when the two-digit codes in the business profession (code 24 and 34) were combined in consideration, the proportions observed in cases (7.8%) and controls (5.5%) were similar (p=0.102).

Table 5.5 Teaching professions in the entire occupation history

SSOC code	Occupation	Control		LN cases		TOTAL	
		n	(%)	n	(%)	n	(%)
23102	Polytechnic lecturer	0	(0.0)	1	(2.9)	1	(1.7)
23201	Pre-university/ secondary school teacher	5	(20.0)	7	(20.6)	12	(20.3)
23300	Primary school teacher	5	(20.0)	5	(14.7)	10	(17.0)
23409	Other special education teacher	0	(0.0)	1	(2.9)	1	(1.7)
23990	Other teaching professional nec	1	(4.0)	8	(23.5)	9	(15.3)
33110	Pre-primary education teachers	3	(12.0)	4	(11.8)	7	(11.9)
33202	Arts and crafts school teachers	1	(4.0)	0	(0.0)	1	(1.7)
33203	Computer school teachers	1	(4.0)	0	(0.0)	1	(1.7)
33209	Other extra-curriculum teachers	1	(4.0)	1	(2.9)	2	(3.4)
33910	Private tutors	8	(32.0)	5	(14.7)	13	(22.0)
33991	Relief teachers	0	(0.0)	2	(5.9)	2	(3.4)
	TOTAL (%)	**25**	**(42.4)**	**34**	**(57.6)**	**59**	**(100.0)**

On average, among the 59 teachers, 23 male teachers had taught 15.7 years (SD 16.2) which was slightly longer than the 36 female teachers (13.5 years, SD 13.6). **Table 5.6** shows the OR for those who had ever been in these selected occupations versus other occupations for NHL and HL separately. Among the 31 teachers with NHL, 22.6% taught in upper secondary schools, with equal proportion teaching in and primary, pre-primary schools and private tutors (12.9%), and the rest engaged in other forms of teaching (38.7%). As compared to non-teachers, teachers had a significantly higher risk of NHL (adjusted OR 2.04, 95%CI 1.12-3.71). Teachers who had taught for 1-10 years had significantly higher risk of NHL (adjusted OR 2.43; 95%CI 1.11-5.33), but we did not observe an elevated risk for those who reported a teaching duration of more than 10 years.

There was no difference in association between those who had ever been machine operators as compared with those who had never been machine operators. Those who had ever worked as labourers and related workers had a 38% decreased in risk in NHL (95%CI 0.41-0.94). We did not detect any association between any of these occupations and HL.

Table 5.6 Adjusted odds ratios and 95% CIs for the association between the 3 selected occupations with the risk of lymphoma.

SSOC code	Occupation	Controls		Non-Hodgkin lymphoma					Hodgkin lymphoma				
		n	(%)	n	(%)	OR	(95% CI)‡	*p*-value	n	(%)	OR	(95% CI)‡	*p*-value
23,33	Never worked as teachers	724	(96.7)	397	(92.8)	1.00	(referent)		55	(94.8)	1.00	(referent)	
	Teachers	25	(3.3)	31	(7.2)	**2.04**	**(1.12-3.71)**	**0.020**	3	(5.2)	1.38	(0.38-4.98)	0.620
	Teaching duration												
	1-10 years	15	(2.0)	17	(4.0)	**2.43**	**(1.11-5.33)**	**0.026**	3	(5.2)	2.25	(0.58-8.71)	0.241
	>10 years	10	(1.3)	14	(3.3)	1.61	(0.66-3.92)	0.298	0	(0)			
82	Never worked as machine operators	595	(79.4)	355	(82.9)	1.00	(referent)		53	(91.4)	1.00	(referent)	
	Machine operators	154	(20.6)	73	(17.1)	0.82	(0.58-1.15)	0.251	5	(8.6)	0.41	(0.16-1.07)	0.069
93	Never worked as labourers	648	(86.5)	390	(91.1)	1.00	(referent)		55	(94.8)	1.00	(referent)	
	Labourers	101	(13.5)	38	(8.9)	0.62	(0.41-0.94)	0.024	3	(5.2)	0.44	(0.13-1.46)	0.183

n, number of subjects; CI : confidence intervals; *P*, p-value from logistic regression.

Code 23, 33 includes university, polytechnic, upper secondary, secondary and primary education teachers, special education teachers, school principals or not elsewhere classified.

Code 82 includes machine operator supervisors and general foremen, machine operators of metal products, mineral products, chemical products, rubber products, plastics or wood products, printing, binding and paper products, textile products, food products, assemblers and quality checkers, or machine operators not elsewhere classified.

Code 92 includes agricultural and fishery labourers, manufacturing labourers, construction labourers, transport labourers or related workers not elsewhere classified.

‡ OR, odds ratio adjusted for age (continuous), gender (male/female); ethnicity (Chinese/Malay/Indian), housing type (Public housing ≤3rooms/ Public housing >3rooms/Private housing/Others) and family history of cancer in the first degree relatives (yes/no) in multiple logistic regression model.

5.5 Discussions

Among all epidemiological studies on occupations, none of a specific agent has been suggested in the causal linkage with lymphoma. Most of the problems occurred in these studies, including the difficulty in correct measure of exposure to the agent, or multiple exposures to these agents which may result in synergistic effects. Therefore we screened all occupations reported in the Singapore Lymphoma Study using separate criteria, and identified 3 occupations in Singapore which may have higher chance of developing NHL as compared with the rest of occupations. We have found that teachers appear to have a two-fold elevated risk of NHL as compared with non-teachers.

As early as 1983, there have been reports of an increased standardized cumulative incidence ratio (SIR) for NHL among teachers (Dubrow & Wegman 1983). In a large registry-based analysis in Sweden, researchers used the Swedish Cancer-Environmental Registry to link cancer incidence during 1961 to 1979 with occupational information from the 1960 census; this study reported an SIR among school teachers of 2.1 ($p<0.05$). When they included specific occupations within this industry they found that "school teacher in other education" had an SIR of 3.8 ($p<0.05$) (Linet *et al.* 1993). It was not mentioned in the manuscript what 'other education' involved. This study, being registry based, had no additional information on exposures and duration of employment for one to examine the possible etiological cause for the association. The authors commented that "whether carcinogenic exposures occur among these workers is not clear, although socioeconomic and dietary factors may also be important" (Linet *et al.* 1993). Boffetta and de Vocht (2007) conducted a meta-analysis based on 19 reported studies to provide an update on occupation and

the risk of non-Hodgkin lymphoma. They reported an increased risk for the teaching profession (RR 1.47, 95% CI 1.34-1.61) among other occupations.

Our study would support the hypothesis of a viral aetiology of NHL. Teachers are known to come into contact with students frequently in the course of their work. In Singapore, the ratio of teacher to student could be as high as 1:40; especially in the 1960's and 1970's. Infectious mononucleosis has been around in Singapore since the 1950's and is quite common among the children in the community (Wong *et al.* 1982). It is thus plausible for the teachers to be infected with Epstein-Barr virus (EBV) in their daily contact with children as the transmission is generally by infected saliva. Instead, as compared to non-teachers, those who had ever been teachers and had taught for between 1-10 years duration had a two-fold increase in NHL risk in our study. However, the OR for >10 years duration was not significant when compared with non-teachers, and a dose response relationship was not found. This observation is understandable given that we are looking at an infectious agent and thus cumulative exposure and health effect would not be an important aspect in this finding.

Our findings are in agreement with other studies which also reported no statistically significant differences between teachers in primary or secondary education (Boffetta & de Vocht 2007; Miligi *et al.* 1999). We did not observe any marked difference in the distribution of teachers with NHL in different levels of teaching. What is interesting though is that among the 31 ever-teachers cases diagnosed with NHL, 48.4% were teaching in the secondary, primary and pre-primary schools. The students from these groups would be in their adolescent and early childhood which placed them in the prevalent group for infectious

mononucleosis. Infectious agents are close to being regarded as established agents for NHL with EBV as an important example. EBV is generally acquired in early childhood in developing countries while in developed countries it is more prevalent among the adolescents (Engels 2007).

Working in the agricultural and fishery industry were the least common occupations reported in our study. We did not detect any associations between NHL and farmers although studies have found strong associations (Boffetta & de Vocht 2007; Linet *et al.* 1993; Schenk *et al.* 2009). This is not surprising as Singapore is not an agricultural country and has never been given its small land area (710 square kilometres). Likewise, we did not find any association between NHL and industrial workers (viz. printers, cleaners), which was also reported in other studies (Boffetta & de Vocht 2007; Mester *et al.* 2006; t Mannetje *et al.* 2008). It could be possible that the workers in Singapore may not be exposed to significant level of the chemicals and/ or agents which were strictly monitored and under surveillance by the Workplace Safety and Health Act.

We do not have an explanation for the observed NHL risk reduction among labourers and related workers. This is a diverse group of labourers requiring physical efforts and use of simple hand-held tools during every day work; including odd job workers in transport, manufacturing and construction sites, and in agricultural and fishery area. However, there were only 42 lymphoma cases and 101 controls in this group, the sample size is too small to further investigate more specific groupings. We also did not detect any associations with HL subtypes. This could be due to small sample size as in

other case-control studies, and we could not identify any specific agents or exposure that may be unique in the HL.

In summary, based on the occupational history we collected from the Singapore Lymphoma Study, the current analysis provided us an overview of the common occupations in Singapore where the study population were worked as. The results of our analysis suggested excess NHL risk in the teaching profession, but provided little evidence on the association with machine operators and labourers. Further specific studies on the occupations in relation to industry exposures are needed.

5.6 Strength and limitations of occupational analysis

Strength of occupational analysis

The detailed occupational history was collected by standard questionnaire for all cases and controls in this study. The questionnaire was modified from the EpiLymph questionnaire for local context, and thus it was comparable with previous studies in other populations. We marked down a detail description of that full time work, and chemical exposures they faced in every job during interview. This helps us to correctly identify the occupational title for analysis, which based on the job description but not only rely on the title provided by the company. The occupations were coded using the standardized occupational classification in Singapore (2006) for local context.

We did not recruit any hospital controls who were admitted as a result of industrial accidents. There were no established association between

occupational exposures with lymphoma known in the general population. We collected every single job since they graduate from school, as long as it lasted over 1 year. Therefore we have no reasons to believe the participants recall their previous occupations differently, and influenced by their current illness. We have monitored and eliminated the recall bias in this retrospective study.

Limitations on occupational analysis

We acknowledged that under the same occupational title, the environmental exposure varies across different industry. For example, the exposure for cleaner working at industrial chemical plant would be very different from those who work in residential estates. Therefore the wide range of environmental exposure may even out the effects and draw the risk estimates towards null.

Furthermore, the literature review on occupational analysis was very specific with regards to chemicals the study subjects were exposed to and its association with a particular subtype of lymphoma. However, many of the low skilled workers did not know much about the chemicals they worked with years ago, and they are not willing to provide details about the company they used to work in, therefore we were not be able to collect detail information on the potential hazards they were exposed to in each occupation. Due to a lack of *a priori* knowledge on the induction period between exposure to potential hazards and diseased state from the literature, we do not have enough sample size to make specific analysis based on all these factors suggested.

Chapter 6

Association between sun exposure and the risk of lymphoma

As mentioned in **Chapter 1**, the parallel trends of non-melanoma tumours and lymphoma were noticed in the past decade. Ever since, the solar ultraviolet (UV) radiation have been suggested as a common risk factor for both skin cancer and lymphoma.

Ultraviolet radiation (wavelengths 100-400nm) is a naturally occurring electromagnetic radiation emitted by the sun, which divided into UV-A, UV-B and UV-C rays. High energy, short wave UV-C rays (wavelength 100-280nm) are absorbed by dioxygen in Earth's atmosphere. Most of the solar radiation reach the Earth's surface are long wave UV-A rays (wavelengths 315-400nm) and ~10% are UV-B rays (wavelength 280-315nm) (WHO).

UV-A and UV-B are of major importance to human health, and is a two-way sword to human beings. Ultraviolet radiation is a known carcinogen by IARC. Over-exposure to ultraviolet radiation may result in acute or chronic health problems on the eye, skin or in immune system, e.g. cataract, melanoma (El Ghissassi *et al.* 2009; Halliday *et al.* 2011; WHO). Small amount of UV exposure on human skin is crucial as it is our major source of vitamin D_3 production, which is critical for development, growth and maintenance of calcium homeostasis. Rickets is a skeletal deformities disease associated with vitamin D deficiency, and was epidemic in the 19th century (Holick 2003; Holick 2006).

The amount of ultraviolet radiation we received on Earth is affected by several factors. All UV-C and majority of UV-B are blocked by ozone layer. Only a portion of the sunlight is UV, and this portion reduces with sun angles, that is, the less UV at geographical locations away from Equator as distance travelled increases. Others factors include high cloud cover, low altitude, at early morning or late afternoon hours, or during winter are situations with less UV radiation reaches the ground (Kimlin 2008). The ultraviolet radiation levels are monitored by meteorological offices in many countries, and report as the Global Solar UV Index (WHO).

6.1 Literature review on sun exposure and the risk of lymphoma

Studies on the association between sun exposure and the risk of lymphoma are summarized in **Table 6.1**. In epidemiology studies using ***area of residence*** as a measurement for ambient UV exposure, positive associations were found between UV radiation at various geographical latitudes and incidence and mortality from NHL (Bentham 1996; Bertrand *et al.* 2011; Langford *et al.* 1998; Uehara *et al.* 2003). However, the association was either not supported (Hartge *et al.* 1996; Newton 1997; Waltz & Chodick 2008) or inversely reported (Boscoe & Schymura 2006; Chang *et al.* 2011; Grant 2002; Hu *et al.* 2004) in other studies.

Studies on ***individual sun exposure*** levels have been investigated in many case-control studies. A protective effect of leisure-time sun exposure on NHL was generally reported (Boffetta *et al.* 2008; Grandin *et al.* 2008; Hughes *et*

al. 2004; Kelly *et al.* 2010; Kricker *et al.* 2008; Soni *et al.* 2007). These exposures included outdoor leisure activities, vacation at sun-exposed locations, or use of sunbed or tanning booth etc. In the pooled analysis of case-control studies conducted by the InterLymph consortium, a 23% reduction in risk of NHL was found for men and women in the highest quartile of recreational sun exposure with intermittent patterns of exposure, but there was no association between the risk of NHL and non-recreational sun exposure (Kricker *et al.* 2008). The beneficial effect of sun exposure was suggested as a result of vitamin D production after sun exposure.

Several studies have also examined the incidence and mortality of NHL with occupational sun exposure. An increased risk of NHL with outdoor occupation was found in 2 independent case-control studies in Sweden (OR 1.1, 95%CI 1.0-1.2) (Smedby *et al.* 2005) and US Connecticut women (OR 1.8, 95%CI 1.0-3.4) (Zhang *et al.* 2007). Other studies reported no association with NHL overall (Hughes *et al.* 2004; Kelly *et al.* 2010; Kricker *et al.* 2008; Weihkopf *et al.* 2007). A reduced risk of DLBCL subtype with occupational exposure to natural UV radiation was reported in a European study (OR 0.72, 95%CI 0.54-0.97) (Boffetta *et al.* 2008).

UV exposure and pigmentary factors

Melanin is the primary determinant of human skin colour, it is also found in hair and pigmented tissue of the eye. Upon UV irradiation, melanocytes located at the lower level of the skin will produce melanin to the skin's surface, i.e. darker skin colour, to absorb UV and reflects extra UV-B photons by entering the dermis as a natural protective mechanism. The tone of human skin is determined by gene. Africans are generally darker than Europeans, and Asians are usually somewhere between them.

The associations between pigmentary factors and lymphoma risk were inconsistent in the literature. Compared with those with brown eyes, those with light eyes were reported to have increased NHL risk (Hughes *et al.* 2004; Smedby *et al.* 2005) or decreased NHL risk (Hartge *et al.* 2006; Veierod *et al.* 2010), while others did not support an association (Boffetta *et al.* 2008; Grandin *et al.* 2008).

UV exposure and sunburn history

Sunburn is caused by an intense amount of sunlight exposure to skin, or long period of exposure, thus it is another surrogate for sun exposure. However, a person's natural skin colour has an impact on their reaction to exposure under sun, the degree of sunburn varies on the skin sensitivity. In a Swedish case-control study, sunburn at 5-10 years before interview was inversely associated with NHL risk (p-trend=0.003) (Smedby *et al.* 2005) but this association was not found in any other studies (Grandin *et al.* 2008; Kelly *et al.* 2010).

Many studies in the West have investigated the association between sunlight and the risk of lymphoid neoplasms. However, most of these studies conducted in temperate countries where ultraviolet radiation is relatively low and varies across the year. The primary aim of this study was to evaluate the association between the risk of lymphoid neoplasms and sun exposure in a tropical country, with constant and high ultraviolet index throughout the year.

Table 6.1 Sun exposure and risk of lymphoma in cohort and case-control studies since 1996

Reference	Country (study)	Period	Study design	Sun exposure measure*	Subtype	Risk estimates	(95% CI)
Bentham (1996)	England & Wales	1968-1985	Ecological (Cancer registry)	• Residential latitude in high UV radiation	NHL	1.16	(1.14-1.17)
Hughes *et al.* (2004)	Australia	2000-2001	Case-control	• Exposed on working days	NHL	0.95	(0.68-1.33)
				• Exposed on nonworking days	NHL	0.47	(0.34-0.66)
				• Lifetime occupational exposure	NHL	1.21	(0.87-1.69)
				• Vacation (in warmer and cooler months)	NHL	0.60	(0.43-0.85)
Smedby *et al.* (2005)	Sweden & Denmark (SCALE)	1999-2002	Case-control	• Sunbathing >4 times/week (5-10yrs ago)	NHL	0.70	(0.60-0.90)
				• >20 times sun vacations abroad	NHL	0.70	(0.60-0.80)
Hartge *et al. (2006)*	USA (NCI-SEER)	1998-2000	Case-control	• Exposure >28 hrs. in the mid-day sun in the last 10 yrs.	NHL	0.73	(0.46-1.15)
				• Ever use sunlamp/tanning booth	NHL	0.88	(0.66-1.19)
Soni *et al. (2007)*	USA (Nebraska)	1999-2002	Case-control	• Exposure >30 hours/week	NHL	0.70	(0.50-1.10)
				o Farmers only	NHL	0.60	(0.30-0.90)
Weihkopf *et al.* (2007)	Germany	1998-2003	Case-control	• Vacations at sun-exposed location	LN	0.60	(0.40-0.80)
Zhang *et al. (2007)*	USA (Connecticut)	1996-2000	Case-control	• Having suntan	NHL	1.50	(1.00-2.40)
				• Spending time in strong sunlight during summer	NHL	1.70	(1.20-2.40)
				• Ever spending time in tropics	NHL	1.20	(1.00-1.50)

*Measurement comparisons are the highest exposure category vs lowest/no exposure category, unless specified

Table 6.1 (cont.)

Reference	Country (study)	Period	Study design	Sun exposure measure*	Subtype	Risk estimates	(95% CI)
Boffetta *et al. (2008)*	(EpiLymph)	1998-2003	Meta-analysis of 5 case-control studies	• Sunlamp use >25 times • Free days during childhood • Free days during adulthood	NHL NHL NHL	0.69 1.07 0.76	(0.51-0.93) (0.81-1.43) (0.61-0.95)
Kricker *et al.* (2008)	(InterLymph)	1995-2005	Meta-analysis of 11 case-control studies	• Composite total sun exposure • Composite recreational sun exposure	NHL NHL	0.87 0.76	(0.71-1.05) (0.63-0.91)
Freeman *et al. (2010)*	USA (USRT study)	1994-2005	Nested case-control	• Personal exposure (>21hrs/week) • Summer ambient exposure • Winter ambient exposure • Average annual ambient expo.	NHL NHL NHL NHL	0.91 0.76 0.69 0.70	(0.48-1.74) (0.43-1.33) (0.41-1.18) (0.41-1.20)
Kelly *et al. (2010)*	USA (Rochester)	2002-2005	Case-control	• Exposure >8 hours/week (5-10yrs ago) • Sunbathing >1/week (5-10yrs ago)	LN NHL LN NHL	0.47 0.44 0.28 0.27	(0.12-1.90) (0.11-1.84) (0.10-0.79) (0.09-0.78)
Veierod *et al. (2010)*	Sweden & Norway (The Norwegian-Swedish Women's Lifestyle & Health Cohort Study)	1991-2007	Cohort	• Sunbathing vacations ≥1week/yr (age 10-39) • Use of artificial tanning device ≥once/month in 1-3 decades (age 10-39)	NHL NHL	1.00 0.93	(0.64-1.54) (0.52-1.68)
Bertrand *et al. (2011)*	USA (Nurses' Health Study)	1976-2006	Cohort	• Residing in high ambient UV radiation	NHL	1.21	(1.00-1.47)
Chang *et al. (2011)*	USA (California Teachers Study)	1995-2007	Cohort	• Minimum residential UV radiation [≥5100 vs <4915 W-h/m^2]	NHL	0.58	(0.42-0.80)

*Measurement comparisons are the highest exposure category versus lowest/no exposure category, unless specified

6.2 Definition of sun exposure-related variables

The detail of the study has been described in **Chapter 4**. In brief, the Singapore Lymphoma Study is a hospital-based case-control study in Singapore from 2004 to 2008. Malignant lymphoma patients and hospital participants were interviewed using structured standardized questionnaire by trained research staff.

In this section, we described detailed information on sun sensitivity and pigmentary related characteristics, as well as outdoor sunlight exposures for both recreational and occupational purposes which were collected to evaluate the association between sun exposure and the risk of lymphoma.

Sun sensitivity and Pigmentary variables: Participants were asked about skin colour (white or light tan, tan, dark brown or black) on the inner side of the arm, eye colour (black or dark brown, light brown, other) and natural hair colour (black, dark brown, light brown, other). Other variables included history of sunburn (frequency and age at first sunburn), the use of sun protection including hat, sun-cream, long sleeves or umbrella; and the skin reaction to strong sunlight without any protection (severe sunburn with blistering, painful sunburn followed by peeling, mildly burnt and some tanning, go brown without sunburn).

Leisure sun exposure variables: The number of hours spent under the sun on leisure activities were used as a measure for sun exposure. Participants were asked how many hours they spent outdoors regularly between 9am and 5pm, not staying under any shade on activities such as swimming,

sailing, jogging, playing tennis etc., on school days or weekends in childhood (i.e. <20 years of age), and on working days or rest days in adulthood (i.e. 20 years of age and above).

Measures of recreational sun exposure were constructed for the statistical analysis as follows: Daily exposure was defined as "regular" if at least 30 minutes per day were spent on outdoor recreational activities on a regular basis; separately for (1) **SCHOOL DAYS** and (2) **NON-SCHOOL DAYS** in childhood, (3) **WORKING DAYS** and (4) **NON-WORKING DAYS** in adulthood. The daily exposure was capped at 8 hours per day. Weekly exposure was calculated by adding up the daily exposure reported over 5 school days and 2 non-school days in childhood (i.e. **CHILDHOOD PER WEEK**), and 5 working days and 2 non-working days in adulthood (i.e. **ADULT PER WEEK**). The weekly exposure was capped at 56 hours per week. The unexposed group served as the reference category.

Occupational sun exposure variable: As in **Chapter 5**, we asked for a complete occupational history of jobs held which lasted at least one year or more. Information included the year when employment started and ended, and the average daily hours of exposure to the sun for every job. Participants were defined as working outdoor if they had spent at least 30 minutes outside under the sun without any shade (between 9am to 5pm). We categorized participants into '**INDOOR WORK ONLY**' workers, and those who spent all or part of their working hours outdoors (i.e. '**MIXED INDOOR ± OUTDOOR**').

6.3 Statistical analysis

The distribution of sun exposure behaviours between males and females were compared by simple chi-square test for categorical variables and Student's *t*-test for continuous variables.

As in **Chapter 5**, an unconditional logistic regression model was used to quantify the effect of outdoor sun exposure on the risk of malignant lymphoma via the OR estimate and its 95%CI. In addition to potential confounders such as age, gender and ethnicity, we further consider the inclusion of BMI and skin colour (white or light tan/tan/dark brown or black) in the model. We further assessed the interaction effect of sun exposure and gender in the multivariable model. Further adjustment of hair colour, skin sensitivity, marital status, height, weight, and energy expenditure on physical activities did not change the risk estimates materially and were not included in the final models.

6.4 Results

Sun exposure behaviour between males and females

The sun exposure factors (n=1,357, 799 males and 558 females) and pigmentary-related behaviour (n=1,362, 802 males and 560 females) were significantly different between genders in our study population (**Table 6.2**).

Table 6.2 Sun exposure and pigmentary-related factors by gender

	Males No (%)	**Females** No (%)	***p*-value**
Case	315 (38.9)	226 (40.3)	0.603
Control	495 (61.1)	335 (59.7)	
Natural hair colour			
Black	788 (98.3)	533 (95.2)	0.001
Brown (Dark/light)	14 (1.8)	27 (4.8)	
Eye colour			
Black/Dark Brown	764 (95.3)	547 (97.9)	0.012
Light Brown	38 (4.7)	12 (2.2)	
Skin colour			
White/Light tan	280 (34.9)	333 (59.6)	<0.001
Tan	430 (53.6)	194 (34.7)	
Dark brown/Black	92 (11.5)	32 (5.7)	
History of sunburn			
Never	419 (52.2)	389 (69.6)	<0.001
Ever	383 (47.8)	170 (30.4)	
Mean age at first sunburn (SD)	19.5 (10.3)	17.7 (7.2)	0.039
Skin reaction to strong sunlight with no protection			
Go brown only	582 (72.7)	448 (80.1)	0.006
Mildly burnt and tanned	48 (6.0)	23 (4.1)	
Painful burn and peeling	156 (19.5)	85 (15.2)	
Severely burnt and blistering	15 (1.9)	3 (0.5)	
Mean recreational sun exposure (SD)			
On childhood school days (hrs/day)	2.13 (2.2)	1.16 (1.8)	<0.001
On childhood non-school days (hrs/day)	2.57 (2.7)	1.17 (2.1)	<0.001
Childhood weekly (hrs/week)	15.76 (15.6)	8.14 (12.6)	<0.001
On adult working days (hrs/day)	0.53 (1.2)	0.27 (0.8)	<0.001
On adult weekends (hrs/day)	0.97 (1.8)	0.51 (1.4)	<0.001
Adult weekly (hrs/week)	4.59 (8.2)	2.38 (5.7)	<0.001
Mean occupational sun exposure (SD)			
On adult working day (hrs/day)	2.17 (2.6)	0.44 (1.3)	<0.001
TOTAL	**810**	**561**	

As compared with male subjects, female subjects were lighter in skin complexion (59.6% white/light tan versus 34.9% in males), less likely to experience sunburn (30.4% versus 47.8%), and had more sensitive skin reaction to strong sunlight without protection (15.7% vs. 21.4%). Male subjects spent more time under the sun, for recreational or occupational purposes, during both childhood and adulthood. The weekly exposure in adulthood was 4.59 hours (SD 8.2) in men and 2.38 (SD 5.7) in women; corresponding figures for childhood exposure are 15.76 hours (SD 15.6) for boys, and 8.14 hours (SD 12.6) for girls. These variables supported the hypothesis that female spending less time under the sun.

Pigmentary characteristics and risk of lymphoma

The associations between pigmentary and sun sensitivity characteristics and risk of malignant lymphoma were shown in **Table 6.3**. Limited variation was observed in eye and hair colour since the majority of subjects were reported as having black/dark brown eyes (96.3%) and black hair (97.0%). Although the number of persons with natural lighter-coloured hair (brown, as opposed to black) was small, this characteristic conferred a two-fold risk of all lymphomas combined (OR 1.95, 95%CI 0.98 – 3.89). Forty per cent of the study populations have ever had sunburn in their lifetime; 16.9% of cases and 20.4% of controls experienced painful/severe burn after repeated sun exposure. There was no association between skin colour and sun sensitivity (sunburn history, age at first sunburn or skin reaction to strong sunlight without protection) and risk of either NHL or HL.

Table 6.3 Association between pigmentary and sun sensitivity and risk of lymphoid malignancies in the Singapore Lymphoma Study

Pigmentary and sun sensitivity characteristics	Controls		Lymphoid neoplasms				non-Hodgkin lymphoma				Hodgkin Lymphoma			
	No	(%)	No	(%)	OR[a]	(95% CI)	No	(%)	OR[a]	(95% CI)	No	(%)	OR[a]	(95% CI)
Hair colour (natural)														
Black	810	(97.7)	511	(95.9)	1.00	(ref)	441	(96.3)	1.00	(ref)	68	(93.2)	1.00	(ref)
Brown (Dark/light)	19	(2.3)	22	(4.1)	1.95	(0.98-3.89)	17	(3.7)	1.98	(0.93-4.19)	5	(6.9)	2.16	(0.67-6.94)
Eye colour														
Black/Dark Brown	799	(96.4)	512	(96.2)	1.00	(ref)	439	(96.1)	1.00	(ref)	71	(97.3)	1.00	(ref)
Light Brown	30	(3.6)	20	(3.8)	1.38	(0.68-2.78)	18	(3.9)	1.42	(0.67-3.00)	2	(2.7)	1.37	(0.30-6.24)
Skin colour														
White/Light tan	350	(42.2)	263	(49.4)	1.00	(ref)	240	(52.5)	1.00	(ref)	23	(31.5)	1.00	(ref)
Tan	383	(46.2)	241	(45.3)	0.90	(0.69-1.19)	196	(42.9)	0.79	(0.59-1.06)	43	(58.9)	1.59	(0.89-2.86)
Dark brown/Black	96	(11.6)	28	(5.3)	0.65	(0.34-1.21)	21	(4.6)	0.67	(0.33-1.36)	7	(9.6)	0.57	(0.17-1.97)
History of sunburn														
Never	490	(59.1)	318	(59.8)	1.00	(ref)	281	(61.5)	1.00	(ref)	35	(48.0)	1.00	(ref)
Ever	339	(40.9)	214	(40.2)	0.97	(0.74-1.28)	176	(38.5)	0.98	(0.73-1.32)	38	(52.1)	1.00	(0.56-1.77)
Skin reaction to strong sunlight with no protection														
Go brown only	614	(74.2)	416	(78.2)	1.00	(ref)	365	(79.9)	1.00	(ref)	49	(67.1)	1.00	(ref)
Mildly burnt and tanned	45	(5.4)	26	(4.9)	0.82	(0.47-1.43)	22	(4.8)	0.90	(0.49-1.63)	4	(5.5)	0.62	(0.20-1.87)
Painful burn and peeling	158	(19.1)	83	(15.6)	0.76	(0.54-1.06)	64	(14.0)	0.70	(0.49-1.01)	19	(26.0)	1.05	(0.57-1.93)
Severely burnt and blistering	11	(1.3)	7	(1.3)	0.65	(0.20-2.16)	6	(1.3)	0.56	(0.15-2.13)	1	(1.4)	1.28	(0.15-10.8)

Abbreviation: ref, referent; * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Numbers did not add up to 829 controls and 533 cases due to missing data.

[a] OR, odds ratio adjusted for age (continuous), gender (male/female), ethnicity (Chinese/Malay/Indian), education (never/<6/7-10/>10yrs), current housing types (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no) in multiple logistic regression model.

Use of sun protections

The habit of using sun protection during leisure outdoor activities was not common in this study population. Only 5.1% of controls and 2.3% of cases reported they ever use any in childhood, and 9.3% of controls and 8.4% of cases in adulthood. Among the adults who had ever used sun protection, this was more prevalent in females, although only half of them had engaged in any form of regular leisure exercise outdoor. The prevalence of using sun protection was very low in this study population, only 4.0% of participants had ever used sun protection during childhood (3.6% used in school days and 3.4% in non-schooldays). The usage was slightly higher in adulthood (9.1% ever users (6.2% on working days and 7.6% on non-working days).

Occupational sun exposure

As in **Chapter 5**, 749 controls and 487 cases reported detailed occupation history. Of these, 745 controls and 482 cases reported the number of hours spent working under the sun in each job for the current analysis. On average, cases and controls spent 1.4 hours/day (SD 2.3) and 1.5 hours/day (SD 2.3) working outdoors respectively. Participants who had ever engaged in outdoor occupations had a decreased risk of NHL overall (OR 0.75, 95%CI 0.55 – 1.03) and for B-cell NHL subtypes (OR 0.73, 95%CI 0.53 – 1.02) as compared with those who only worked indoors (**Table 6.4**).

Table 6.4 Association between outdoor sun exposure for recreational or occupational purposes and risk of lymphoid malignancies in the Singapore Lymphoma Study, 2004-2008

Outdoor sun exposure	Ctrl	Lymphoid neoplasms			non-Hodgkin lymphoma									Hodgkin lymphoma		
					NHL			B-cell NHL			T-cell NHL					
	No	No	OR[a]	(95% CI)	No	OR[a]	(95% CI)	No	OR[a]	(95% CI)	No	OR[a]	(95% CI)	No	OR[a]	(95% CI)
Occupational																
Indoor work only	372	262	1.00	(ref)	233	1.00	(ref)	207	1.00	(ref)	26	1.00	(ref)	29	1.00	(ref)
Mixed indoor ± outdoor work	373	220	0.76	(0.56-1.02)	192	0.75	(0.55-1.03)	162	0.73	(0.53-1.02)	28	1.10	(0.55-2.21)	27	0.76	(0.39-1.47)
Regular recreational																
Daily																
Childhood on School days																
No regular exposure	387	268	1.00	(ref)	240	1.00	(ref)	215	1.00	(ref)	25	1.00	(ref)	27	1.00	(ref)
>30 mins exposure /day	434	246	0.78	(0.59-1.04)	200	0.80	(0.60-1.09)	169	0.76	(0.56-1.04)	32	1.46	(0.74-2.90)	45	0.80	(0.45-1.43)
Childhood on Non-school days																
No regular exposure	385	295	1.00	(ref)	261	1.00	(ref)	236	1.00	(ref)	25	1.00	(ref)	33	1.00	(ref)
>30 mins exposure /day	436	219	**0.62**	**(0.47-0.81)****	179	**0.62**	**(0.46-0.83)****	148	**0.56**	**(0.41-0.77)****	31	1.35	(0.70-2.60)	39	0.69	(0.40-1.22)
Adult on Non-working days																
No regular exposure	563	394	1.00	(ref)	353	1.00	(ref)	302	1.00	(ref)	51	1.00	(ref)	40	1.00	(ref)
>30 mins exposure /day	241	116	0.76	(0.57-1.02)	95	**0.70**	**(0.51-0.97)***	90	0.83	(0.60-1.16)	5	**0.19**	**(0.06-0.54)****	21	1.03	(0.57-1.87)
Weekly [b]																
Childhood per week																
No regular exposure	329	241	1.00	(ref)	217	1.00	(ref)	195	1.00	(ref)	22	1.00	(ref)	23	1.00	(ref)
>1 hour exposure /week	492	273	**0.73**	**(0.55-0.96)****	223	**0.73**	**(0.54-0.99)***	189	**0.69**	**(0.51-0.95)***	34	1.27	(0.64-2.53)	49	0.80	(0.44-1.46)
Adult per week																
No regular exposure	543	369	1.00	(ref)	331	1.00	(ref)	286	1.00	(ref)	45	1.00	(ref)	37	1.00	(ref)
>1 hour exposure /week	261	141	0.92	(0.69-1.21)	117	0.87	(0.64-1.17)	106	0.96	(0.70-1.31)	11	0.49	(0.23-1.04)	24	1.13	(0.63-2.03)

Abbreviations : Ctrl, control; n, number; ref, reference group; * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Numbers did not add up to 829 controls and 528 cases due to missing data.

[a]OR, Odds ratio adjusted for age (continuous), gender (male/female), ethnicity (Chinese/Malay/Indian), skin colour (white-light tan/tan/dark brown-black), education (never/<6/7-10/>10yrs), current housing types (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no) in multiple logistic regression model. (Further adjustment of hair colour, skin sensitivity, height, weight, MET did not change risk estimates.)

[b]Weekly sun exposure = 5 x school days + 2 x non-school days (age <20yrs); or 5 x working days + 2 x non-working days (age ≥20 yrs)

Recreational sun exposure

During childhood, cases and controls spent, on average, 11.9 hours/week (SD 15.4) and 13.1 hours/week (SD 14.6) respectively, on recreational activities under the sun. The amount of time was reduced substantially to 3.2 hours/week (SD 6.9) and 4.0 hours/week (SD 7.6), respectively, during adulthood.

Compared to those without regular recreational sun exposure, those who regularly spent at least 30 minutes/day outdoors on non-school days during childhood had a 38% reduction in risk of lymphoma. A significant association was observed for NHL (OR 0.62, 95%CI 0.46 – 0.83), and for B-cell lymphoma (OR 0.56, 95%CI 0.41 – 0.77) in particular. Similarly, the risk of NHL among those who reported regular recreational sun exposure in adulthood on non-working days was also significantly reduced (OR 0.70, 95% CI 0.51 – 0.97). For T-cell lymphoma, the observed reduction (OR 0.19, 95% CI 0.06 – 0.54) was based on a small number of cases. In terms of weekly recreational sun exposure, a significant risk reduction was observed consistently for lymphoid neoplasms (OR 0.73, 95%CI 0.55 – 0.96), NHL (OR 0.73, 95%CI 0.54 – 0.99) and B-cell NHL (OR 0.69, 95%CI 0.51 – 0.95) in childhood, but not in adulthood.

The protective effect of childhood sun exposure was more evident in females (**Table 6.5**). There was a 50% to 60% risk reduction in NHL observed in females; on school days (OR 0.54, 95%CI 0.34 – 0.87), non-school days (OR 0.38, 95%CI 0.23 – 0.61), and on combined weekly exposure (OR 0.43, 95%CI 0.27 – 0.68).

Table 6.5 Association between childhood sun exposure and non-Hodgkin lymphoma by gender

Recreational sun exposure in childhood	Males				Females				$P_{interaction}$
	Control	Cases	OR[a]	(95% CI)	Control	Cases	OR[a]	(95% CI)	
Daily									
On School days									
No regular exposure	193	104	1.00	(ref)	194	136	1.00	(ref)	**0.029**
>30 mins exposure/day	300	147	1.03	(0.71-1.49)	134	53	**0.54**	**(0.34-0.87)****	
On Non-school days									
No regular exposure	182	111	1.00	(ref)	203	150	1.00	(ref)	**0.011**
>30 mins exposure/day	311	140	0.82	(0.57-1.17)	125	39	**0.38**	**(0.23-0.61)*****	
Weekly [b]									
No regular exposure	153	84	1.00	(ref)	176	133	1.00	(ref)	**0.006**
>1 hour exposure/week	340	167	0.97	(0.70-1.45)	152	56	**0.43**	**(0.27-0.68)*****	

Abbreviation : ref, referent; OR, odds ratio; CI, confidence intervals; ** P value<0.01 *** P value<0.001.

Numbers did not add up to 829 controls and 453 cases due to missing data.

[a] OR, odds ratio adjusted for age (continuous), ethnicity (Chinese/Malay/Indian), skin colour (white-light tan/tan/dark brown-black), education (never/<6/7-10/>10yrs), housing type (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no) in multiple logistic regression model.

[b] Weekly sun exposure = 5 x school days + 2 x non-school days (age <20yrs);

6.5 Discussions

Our results suggest that in this study population, regular leisure-time sun exposure in both childhood and adulthood are associated with a reduced risk of non-Hodgkin lymphoma. Lower estimated risk was also found in who were darker in skin pigmentation than those who were comparatively fair skinned. The degree of skin pigmentation among the 3 Asian races in Singapore is different from Caucasian populations, according to the Fitzpatrick skin type classification (Fitzpatrick 1988). When stratified by gender, the reduction in risk conferred by regular childhood sun exposure was stronger in females than in males.

Recreational sun exposure

Our findings on the protective association of recreational sun exposure are generally consistent with other studies on personal sun exposure in the West (Boffetta *et al.* 2008; Hartge *et al.* 2006; Kelly *et al.* 2010; Kricker *et al.* 2008; Smedby *et al.* 2005; Soni *et al.* 2007; Weihkopf *et al.* 2007). A case-control study by Hughes *et al* (2004) in Australia was the first to report an inverse association between personal ultraviolet radiation exposure and the risk of NHL. There were reduced risk with exposure on non-working days in adulthood, suggesting that an intermittent pattern of sun exposure might be protective; and the protective effect of year-round sun exposure was greatest during childhood. The InterLymph analysis of 10 case-control studies in the West reported a pooled odds ratio of 0.76 (95%CI 0.63 – 0.91) for recreational sun exposure (Kricker *et al.* 2008). A recent case-control study in Rochester

(Kelly *et al.* 2010) reported a decrease in NHL risk in subjects who had sunbathed more than once per week versus never (OR 0.28, 95%CI 0.10 – 0.79) over the past 10 years. A Scandinavian study also demonstrated a reduced risk in NHL, especially the B-cell type, with increasing adult personal sun exposure, and among subjects who had spent vacations in sunny southern climates (Smedby *et al.* 2005). In contrast, a population-based case-control study of Connecticut women showed an increased risk of NHL among those who reported spending time (between 9am and 3pm) in strong sun during summer (OR 1.7, 95%CI 1.2 – 2.4) (Zhang *et al.* 2007).

In the multi-country InterLymph study, the recreational sun exposures was measured at different time periods in life (e.g. lifetime, age 10-17, age 18-40, and 10 years before diagnosis) (Kricker *et al.* 2008). However, the level of ultraviolet radiation on Earth affects by many factors. These epidemiological studies also measure personal sun exposure behaviours include vacations overseas at sun-exposed areas (Hughes *et al.* 2004; Smedby *et al.* 2005; Veierod *et al.* 2010; Weihkopf *et al.* 2007; Zhang *et al.* 2007), this reflects the effect of sun exposure at a different geographical location. The use of artificial sun-tanning device (Boffetta *et al.* 2008; Hartge *et al.* 2006; Veierod *et al.* 2010) which provide a constant source of artificial ultraviolet radiation, but these two behaviours are more prevalent in the population at higher social economic class. Some studies measured sun exposure behaviour at summer and winter separately (Bertrand *et al.* 2011; Hughes *et al.* 2004). As in the Singapore study, we measured the sun exposure at everyday life behaviour in both childhood and adulthood. Since there is no significant seasonal difference in Singapore, the study populations are exposed under the constant strong ultraviolet radiation.

The reason for the strong association in women is not immediately clear. It is possible that the effect is greater because of the lower baseline exposure in this group, compared with their male counterparts. Our results were supported by the Australian study reported by Hughes *et al.* (2004), that the association of sun exposure and the NHL risk reduction was apparently stronger in women. In our population, the higher exposure hours in childhood than adulthood may be the reason for the apparently stronger effect in childhood, as suggested by the Australian study.

Occupational sun exposure

The average occupational sun exposure reported in our study was comparable with other studies on pterygia and sun exposure in Singapore (Khoo *et al.* 1998; Saw *et al.* 2000). In the study by Khoo *et al* (1998), the control group of 125 subjects spent on average 1.6 hours per day (SD 1.6) at the time of study and 1.9 hours per day (SD 1.8) 5 years before. We detected a marginal protective effect of occupational exposure in adults, although this was not evident in the pooled analysis based on the InterLymph data (Kricker *et al.* 2008). However, EpiLymph reported a similar result, which was only limited to the Diffuse large B-cell lymphoma subtype (OR 0.72, 95%CI 0.54 – 0.97) (Boffetta *et al.* 2008). Most of the studies in the West did not detect any association between occupational sun exposure and NHL risk.

Possible mechanisms of protection

As mentioned earlier, ultraviolet radiation has duel function. It can function as a carcinogen and has immunosuppression functions (Norval 2001), that skin aging and sunburn are mainly caused by DNA-damaging UVA (95% of UV radiation). On the other hand, sun exposure may reduce the risk of lymphoid neoplasms by means of vitamin D-related pathways (Giovannucci 2005).

The main source of vitamin D (cholecalciferol) production in humans is the skin, where it is synthesized from 7-dehydrocholesterol following exposure to UV-B radiation in sunlight (Holick 1994). 7-dehydrocholesterol in skin is converted to previtamin D_2 by UV-B photos, and later metabolized in the liver to 25-hyrdoxyvitamin D [25(OH)D], which is used to determine the serum vitamin D level. 25(OH)D is then metabolized in the kidney to active form 1,25-dihydroxyvitamin D [1,25(OH)D], and is tightly regulated by parathyroid hormone and calcium levels. Vitamin D levels can be directly measured from serum (Holick 2007). Experimental studies have demonstrated that the active form of vitamin D has anti-proliferative and pro-differentiation effects on tumour cells (Studzinski & Moore 1995) and lymphoma cell lines (Hickish *et al.* 1993); and its deficiency might be related to rheumatoid arthritis, Type 1 Diabetes, autoimmune diseases or even cancers (Cutolo *et al.* 2009; Holick 2004; Zella & DeLuca 2003).

Vitamin D production decreases with increasing age (Holick *et al.* 1989; MacLaughlin & Holick 1985), increasing skin colour pigmentation (Clemens *et al.* 1982), or under protective shielding including long sleeve clothing or face veil,

umbrella or sunscreen use (Holick 1994). The duration spent under the sun is directly proportional to vitamin D produced, until the maximum capacity in the skin is reached. Given the same amount of exposure time, those with darker skin would produce much less vitamin D as compared with those with fairer skin, the amount of UV enter the skin is reduced by melanin. However, experiments on pigmentation on sun exposure in the 1980s showed that Indians (with darker skin colour) had the same vitamin D capacity as Caucasians (with fairer skin colour), and they needed longer time of exposure under sun to produce the same quantities (Holick *et al.* 1981; Lo *et al.* 1986).

Since the skin cancer has increased in Singapore in the past few decades, many public health education programmes emphasize on the avoidance of excessive sun exposure (Sng *et al.* 2009). In our study population, only a small proportion of subjects used any sun protection devices during their time spending outdoor. Sun avoidance is common in the fairer skinned and in female participants. Subjects with darker skin were the one spending more time under the sun. As reported by a UK study, the Caucasian females showed low level of 25(OH)D in fair skin types compared to darker skin types due to sun avoidance, although their fairer skin has better efficiency in producing vitamin D under the same amount of exposure time (Glass *et al.* 2009).

Vitamin D insufficiency is common in the world, and it is not limited to only dark skin colour population such as Blacks or Indians. Surveys in Malaysia and India revealed more than 70% of healthy postmenopausal Malay and Indian women had insufficient vitamin D level (25-50nmol/l), which may be related to their darker skin colour (Arya *et al.* 2004; Harinarayan 2005; Rahman *et al.* 2004). Lips (2007) reviewed the serum vitamin D levels in Europe and Asia,

and found more than 80% of Lebanon and Saudi Arabia women were vitamin D deficient (<25nmol/l) due to completely veiled clothing.

The main source of vitamin D comes from skin upon sun exposure, and minority come from diet or dietary supplements sources. To date, epidemiologic studies that have examined the association between self-reported dietary vitamin D intake from food-frequency questionnaires and NHL have yielded null associations (Chang *et al.* 2011; Freedman *et al.* 2007; Hartge *et al.* 2006; Kelly *et al.* 2010; Purdue *et al.* 2010; Soni *et al.* 2007). Hartge's analysis of SEER data supported the significance of residential UV level on the reduction of NHL risk (RR 0.76 per 50 RB-units increase). They did not find an association between vitamin D intake from food or supplements and NHL risk (Hartge *et al.* 2006). This study was later supported by the California Teachers Study (Chang *et al.* 2011). Residential UV radiation levels were associated with reduced risk of overall NHL, but not associated with dietary vitamin D in this cohort study. Both studies suggested that higher routine exposure to UV radiation in the vicinity of residence may reduce the lymphoma risk. Since dietary intake is the minority source of vitamin D, and the lack of an association with risk of lymphoma suggest the effect may not be replaced by diet or vitamin supplements, or possibly an alternate sun exposure-related but vitamin D-independent pathway between ultraviolet radiation and lymphomagenesis. On the other hand, in a nested case-control study, Lim *et al* (2009) reported an inverse association only in cases diagnosed in less than 7 years from the baseline, (highest versus lowest tertile of serum 25(OH)D: OR 0.43, 95%CI 0.23 – 0.83, p-trend=0.01), but not in later diagnosis (OR 1.52, 95%CI 0.82 – 2.80). It suggested the potentially protective effect of vitamin D may only have a short term effect on risk reduction of NHL.

The primary aim of this study was to evaluate whether the previously described effects of sun exposure on the risk of lymphoid neoplasms can be replicated in an Asian population living in the topics. Our study supported the intermittent pattern of recreational sun exposure in both childhood and adulthood, in this Tropical country with constantly high ultraviolet radiation throughout the year. Our study concurred with previous studies on the importance of outdoor solar exposure on lymphoma risk reduction. The possible underlying protection mechanism may be due to the vitamin D produced upon sun exposure, but further studies are needed to understand the mechanisms behind.

6.6 Strength and limitations of sun exposure analysis

The strengths are that the data were collected using standardized techniques, with effort made to maintain comparability with previous questionnaires used in other populations. The multi-centre design provided access to a representative sample of eligible incident cases in this country.

At the same time, we are mindful of the limitations that are inherent in the retrospective nature of this study, and the limited sample size. Specifically, we were unable to make inferences about the effect of sun exposure on Hodgkin lymphoma, and on the T-cell NHL subtypes, although the risk estimates suggested interesting differences. The relatively low participation rate (62.4%) in our hospital controls may introduce a selection bias, but it is unlikely that this is related to sun exposure in a way that would account for the associations observed. And, we acknowledge that reporting and recall bias

could occur in this study, but as the hypothesis regarding sun exposure and lymphoma risk is not widely known in the general population, the differential reporting in sun exposure is unlikely to be related to the respective disease status, and as such we would expect a misclassification to be non-differential.

As sun exposure (and not vitamin D) was the primary exposure studied, we did not include dietary sources of vitamin D. This was due to the relatively low intake of vitamin D-rich food sources in this population, and difficulties in obtaining accurate data on supplement intake, and we recognize that this limits the extent to which we can attribute our findings to a particular biologic mechanism.

Chapter 7

Association between smoking and drinking and the risk of lymphoma

It is well known that lifestyle factors, such as tobacco smoking and alcohol drinking, have contributed to the development of cancers, particularly along the gastrointestinal tract (Anand *et al.* 2008). The role of tobacco smoking and alcohol drinking in lymphoma remains unclear, partly due to small sample size in most of the epidemiological studies reported.

7.1 Literature review on tobacco smoking and lymphoma

Tobacco smoking is practised worldwide for a long time in history, and it becomes popular since cigarettes are manufactured massively in factories. Commonly cigarettes are made from fine-cut tobaccos, wrapped in a paper with or without filters. Nicotine, tar, and numerous hazardous additives are identified in cigarettes. Active smoking produces carbon monoxide, benzene and volatile organic compounds in the exhaled air (IARC 2004). Tobacco smoking and tobacco smoke (main stream or side stream smoke) are classified as "Carcinogenic to human" (Group 1) by the IARC (2012). There is sufficient evidence in human showing smoking are attributed to increased risk of at least 14 types of cancer, e.g. oesophagus, lung, stomach, liver, kidney (Anand *et al.* 2008; IARC 2004). However, the study results reported for lymphoma were conflicting.

Epidemiological studies on cigarette smoking and the risk of lymphoma are summarised in **Table 7.1**. Conflicting results were reported over the years, with some showing elevated NHL risk (Freedman *et al.* 1998; Linet *et al.* 1992; Morton *et al.* 2005a; Talamini *et al.* 2005), while others showing no association (Besson *et al.* 2006b; De Stefani *et al.* 1998; Fernberg *et al.* 2006; Herrinton & Friedman 1998; Monnereau *et al.* 2008; Nieters *et al.* 2008; Willett *et al.* 2004; Zahm *et al.* 1997) . The InterLymph consortium of pooled case-control studies, involving 6,594 cases and 8,892 controls, found a slightly elevated NHL risk with ever smokers (OR 1.07, 95%CI 1.00-1.15) and current smokers (OR 1.10 95%CI 1.00-1.20) (Morton *et al.* 2005a). Compared with non-smokers, heavy smokers who consumed ≥20 cigarette/day (Talamini *et al.* 2005) or ≥50 pack/year (Freedman *et al.* 1998), or long-term smokers who smoked ≥36 years (Morton *et al.* 2005a) also reported with increasing NHL risk. Among NHL subtypes, smoking appeared to be associated with follicular lymphoma in some studies (Besson *et al.* 2003; Herrinton & Friedman 1998; Morton *et al.* 2003a; Stagnaro *et al.* 2004).

Studies on cigarette smoking consistently showed increased risk of HL (Besson *et al.* 2006a; Briggs *et al.* 2002a; Glaser *et al.* 2004; Hjalgrim *et al.* 2007; Nieters *et al.* 2006; Nieters *et al.* 2008; Willett *et al.* 2007). A meta-analysis of 17 studies reported an elevated risk of HL in current smokers (OR 1.35, 95%CI 1.17-1.56, p<0.001), but not former smokers (Castillo *et al.* 2011). In the European multi-centre study, doubled-fold risk of HL was observed in current smokers ≥35 years (OR 2.35, 95%CI 1.52-3.61) only (Besson *et al.* 2006a). HL risk increased linearly with years of smoking and packs smoked per days in the Selected Cancer Study in US (p-trend <0.0001) (Briggs *et al.* 2002a), but no such association was found in the Danish-Swedish case-control study

(Hjalgrim *et al.* 2007). Apart from active smoking, exposure to environmental tobacco smoke in childhood was associated with the risk of lymphoma in young adult females (OR 1.6, 95%CI 1.03-2.4) in a case-control study in US women (Glaser *et al.* 2004).

Table 7.1 Summary of epidemiological studies on tobacco smoking and the risk of lymphoma from 1992

Reference	Country (study)	Period	Study design	Tobacco smoking measure*	Subtype	Risk estimates	(95% CI)
Linet *et al.* (1992)	US (Minnesota)	1967-1986	Cohort	• Ever smokers	NHL	2.10	(0.90-4.90)
				o >20 cig/day	NHL	3.80	(1.40-10.1)
Zahm *et al. (1997)*	US (Nebraska, Iowa/ Minnesota, Kansas)	1979-1983	Case-control	• Ever smokers	NHL	1.00	(0.80-1.10)
De Stefani *et al.* (1998)	Uruguay	1988-1995	Case-control	• Ever smokers	NHL	2.40	(0.90-6.40)
Freedman *et al.* (1998)	US (Selected Cancers Study)	1984-1988	Case-control, men only	• Ever smokers	NHL	1.05	(0.89-1.23)
				o ≥50 pack-years	NHL	1.41	(1.08-1.85)
Herrinton & Friedman (1998)	US (SEER)	1964-1991	Cohort	• Former smokers	FL	1.90	(1.20-2.90)
				• Current smokers	FL	1.40	(0.90-2.20)
Briggs *et al.* (2002a)	US (The Selected Cancer Study)	1984-1988	Case-control, men only	• Ever smokers	HL	1.30	(1.00-1.80)
				• Current smokers	HL	1.80	(1.40-2.50)
Besson *et al.* (2003)	France (Rhone-Alpes)	1999-2001	Case-control	• Current smokers, men only	NHL	0.64	(0.33-1.22)
				• Current smokers, women only	NHL	2.40	(1.19-4.84)
				o ≥31 years	NHL	5.04	(1.40-18.1)
Morton *et al.* (2003a)	US (Connecticut)	1995-2001	Case-control, women only	• Ever smokers	NHL	1.00	(0.80-1.30)
				• Smokers ≥34 pack-years	FL	1.80	(1.10-3.20)
Glaser *et al.* (2004)	US (California Great Bay Area)	1988-1994	Case-control, women only	• Current smokers	HL	2.90	(1.03-8.00)
Stagnaro *et al.* (2004)	Italy (11 areas)	1990-1993	Case-control	• Ever smokers using Blond	NHL	1.40	(1.10-1.70)
Willett *et al.* (2004)	England	1998-2001	Case-control	• Ever smokers	NHL	1.04	(0.85-1.28)
				o start smoking >18 years	NHL	1.08	(0.80-1.46)
				• Smoked ≥40 years	NHL	1.09	(0.73-1.64)
				• Quitted ≥20 years	NHL	0.86	(0.62-1.19)
Morton *et al.* 2005	US + Europe (InterLymph)	1990-2004	Meta-analysis of 9 case-control studies	• Ever smoker (pooled)	NHL	1.07	(1.00-1.15)
				• Current smoker (pooled)	NHL	1.10	(1.00-1.20)

***** Never smokers served as reference

Table 7.1 (cont.)

Reference	Country (study)	Period	Study design	Tobacco smoking measure*	Subtype	Risk estimates	(95% CI)
Talamini *et al.* (2005)	Italy (Pordenone & Naples)	1999-2002	Case-control	• Current, ≥20 cig/day	NHL	2.10	(1.07-4.12)
				o HCV positive	NHL	11.48	(1.11-118.96)
Besson *et al*. (2006a)	Europe (EpiLymph)	1998-2004	Meta-analysis of 6 case-controls studies	• Ever smokers	HL	1.33	(1.02-1.74)
				o Age ≥35 years	HL	1.96	(1.33-2.89)
				o Age <35 years	HL	0.89	(0.60-1.32)
Besson *et al*. (2006b)	Europe (EpiLymph)	1998-2004	Meta-analysis of 6 case-controls studies	• Ever smokers	NHL	1.06	(0.92-1.21)
Fernberg *et al*. (2006)	Sweden	1969-1992	Cohort	• Ever smokers	NHL	1.00	(0.87-1.15)
Lim *et al.* (2007)	US (NIH-AARP)	1995-2000	Cohort	• Current smokers	HL	2.25	(1.03-4.88)
				• Quitter <4 years	HL	4.20	(1.94-9.09)
Willett *et al.* (2007)	England	1998-2003	Case-control	• Ever smokers	HL	1.40	(1.10-1.90)
				• Current smokers	HL	1.70	(1.20-2.30)
				• Ex-smokers	HL	1.00	(0.70-1.60)
Monnereau *et al.* (2008)	France	2000-2004	Case-control	• Ever smokers	NHL	0.90	(0.70-1.20)
Nieters *et al.* (2008)	Europe (EPIC)	1992-2005	Cohort	• Ever smoker	HL	2.14	(1.18-3.87)
				• Current smoker	HL	2.54	(1.30-4.96)
				• Quitter <10 years	HL	2.71	(1.25-5.91)
					NHL	1.25	(1.04-1.50)
Kanda *et al.* (2009)	Japan (Aichi)	1988-2005	Case-control	• Current smokers	NHL	1.27	(1.03-1.57)
				o ≥40 pack-years	NHL	1.48	(1.12-1.95)
Troy *et al.* (2010)	US (PLCO)	1993-2001	Cohort	• Ever smokers	NHL	0.94	(0.84-1.05)
					FL	0.62	(0.45-0.85)
Castillo *et al.* (2011)	-	1971-2005	Meta-analysis of 17 studies	• Current smokers	HL	1.35	(1.17-1.56)
				o >15 pack-years	HL	1.97	(1.53-2.54)

***** Never smokers served as reference

7.2 Literature review on alcohol drinking and lymphoma

The IARC working group reviewed published studies on the association between consumption of alcoholic beverages and risk for 27 human cancer sites (IARC 2010a). Consumption of large quantities of alcoholic beverages increases the risk of cardiovascular diseases and cancers along the gastrointestinal tract (Parry *et al.* 2011; Willett & Trichopoulos 1996).

However, the association on alcohol consumption and the risk of lymphoma is inconsistent in previous reports (**Table 7.2**). While most epidemiological studies of NHL have reported a lower risk of lymphoma in drinkers as compared with non-drinkers (Kanda *et al.* 2009; Klatsky *et al.* 2009; Lim *et al.* 2007; Monnereau *et al.* 2008), this observation was not supported in other studies (Benedetti *et al.* 2009; Besson *et al.* 2006b; Chang *et al.* 2010b; Chang *et al.* 2004; De Stefani *et al.* 1998; Deandrea *et al.* 2007; Polesel *et al.* 2007; Tavani *et al.* 2001; Troy *et al.* 2010; Willett *et al.* 2007; Willett *et al.* 2004).

Moderate inverse relation between ever alcohol drinkers and NHL risk (OR 0.83, 95%CI 0.76-0.89) was reported in the InterLymph study (Morton *et al.* 2005b). A UK cohort study reported an association between increasing levels of alcohol consumption and decreased risk of NHL. As compared with non-drinkers, women drinkers who drank ≥15 standard drinks/week had a 23% reduction in risk of NHL (OR 0.77, 95% 0.62-0.94, p-trend 0.001) (Allen *et al.* 2009). The type of alcoholic drink did not change the risk estimates in some studies (Morton *et al.* 2005b; Nieters *et al.* 2006), but other studies reported a lower risk of NHL in wine drinkers only (Briggs *et al.* 2002b; Morton *et al.* 2003b).

In an European case-control study on HL, a similar protective effect of alcohol was reported in both younger subjects (age<35 years) (OR 0.58, 95%CI 0.38-0.89) and older subjects (age ≥35 years) (OR 0.50, 95%CI 0.34-0.74) (Besson *et al.* 2006a). Gorini *et al* (2007) found a protective effect of alcohol consumption was observed only in non-smokers.

In this chapter, we intend to further understand the above-mentioned modifiable lifestyle-related factors and their association with lymphoid neoplasms. The environmental carcinogens may play an important role in the development of lymphoma in an Asian setting which could be different from the Western society.

Table 7.2 Summary of epidemiological studies on alcohol drinking and the risk of lymphoma from 2001

Reference	Country (study)	Period	Study design	Alcohol drinking measure*	Subtype	Risk estimates	(95% CI)
Tavani *et al.* (2001)	Northern Italy	1981-1994	Case-control	• >7 drinks/week	NHL	1.02	(0.64-1.63)
				• Wine intake (≥7 drinks/day)	NHL	0.85	(0.52-1.39)
				• Beer intake (≥3 drinks/day)	NHL	1.17	(0.73-1.87)
				• Spirits intake (≥3 drinks/day)	NHL	1.55	(0.79-3.05)
Briggs *et al.* (2002b)	US (The Selected Cancers Study)	1984-1988	Case-control, men only	• Drinker w/ >1 wine/day	NHL	0.40	(0.20-0.90)
				o Start wine drinking <16 yrs	NHL	0.30	(0.10-0.80)
				• Beer drinker ≥3 drinks/day	NHL	0.90	(0.60-1.40)
				• Spirits drinker ≥3 drinks/day	NHL	1.10	(0.60-2.10)
Chiu *et al.* (2002)	US (Iowa/ Minnesota, Kansas)	1981-1983	Case-control, men only	• Drinker	NHL	0.80	(0.70-1.10)
				o Family hx of hematolymphoproliferative disorder	NHL	2.80	(1.30-5.90)
Morton *et al.* (2003b)	US (Connecticut)	1995-2001	Case-control, women only	• Drinker >12 drinks/year	NHL	0.82	(0.65-1.04)
				o Wine drinker	NHL	0.75	(0.59-0.96)
				▪ Drink >40 years	NHL	0.63	(0.44-0.91)
				o Any beer drinker	NHL	0.94	(0.71-1.23)
				o Any liquor drinker	NHL	1.04	(0.81-1.33)
Willett *et al.* (2004)	England	1998-2001	Case-control	• Drink of the days/wk	NHL	0.94	(0.70-1.25)
				• Drink >6 units/day	NHL	0.84	(0.52-1.35)
Chang *et al.* (2004)	Sweden (SCALE)	1999-2002	Case-control	• Ever drinker	NHL	1.00	(0.60-1.70)
				o >1.9g EtOH/day in males	NHL	1.80	(1.10-2.90)
Morton *et al.* (2005b)	US + Europe (InterLymph)	1988-2002	Meta-analysis of 9 case-control studies	• Ever drinker (pooled)	NHL	0.83	(0.76-0.89)
				• Current drinker (pooled)	NHL	0.73	(0.64-0.84)
				• Former drinker (pooled)	NHL	0.95	(0.80-1.14)
				• Beer, wine and liquor	NHL	0.76	(0.68-0.84)
Besson *et al.* (2006b)	Europe (EpiLymph)	1998-2004	Case-control	• Drinkers in men only	NHL	0.76	(0.62-0.93)
Deandrea *et al.* (2007)	Northern Italy	1981-1994	Case-control	• Drinker ≥5 drinks/day	NHL	0.91	(0.60-1.38)
					HL	0.66	(0.36-1.23)

* Never drinkers served as reference

Table 7.2 (cont.)

Reference	Country (study)	Period	Study design	Alcohol drinking measure*	Subtype	Risk estimates	(95% CI)
Lim *et al.* (2007)	US (NIH-AARP)	1995-2000	Cohort	• Drinkers with >28 drinks/week	NHL	0.77	(0.59-1.00)
Polesel *et al.* (2007)	Italy	1999-2002	Case-control	• Former drinkers	NHL	0.99	(0.49-2.00)
				• Current drinkers >7 drinks/week	NHL	0.88	(0.51-1.52)
Gorini *et al.* (2007)	Italy (11 areas)	1990-1993	Case-control	• Non-smoking drinkers	HL	0.46	(0.30-0.69)
				o > 20 servings/wk	HL	0.34	(0.15-0.79)
				o >31.7g EtOH/day	HL	0.35	(0.15-0.79)
Willett *et al.* (2007)	England	1998-2003	Case-control	• Drinking frequency	HL	0.80	(0.50-1.30)
Monnereau *et al.* (2008)	France	2000-2004	Case-control	• Ever drinker	NHL	0.70	(0.50-1.00)
					HL	0.50	(0.30-0.80)
				• >21 drinks/week	NHL	0.60	(0.40-1.00)
					HL	0.30	(0.10-0.60)
Allen *et al.* (2009)	UK (Million Women Study)	1996-2001	Cohort, women only	• Women drinking ≥15 drinks/wk	NHL	0.77	(0.62-0.94)
				• Wine drinking only	NHL	0.90	(0.78-1.02)
Benedetti *et al.* (2009)	Canada, Montreal	1979-1985	Case-control	• >7 drinks/week	NHL	0.74	(0.48-1.14)
					HL	1.12	(0.46-2.74)
Kanda *et al.(2009)*	Japan (Aichi)	1988-2000	Case-control	• Heavy frequent drinker	NHL	0.70	(0.53-0.93)
		2001-2005			NHL	0.40	(0.23-0.68)
Klatsky *et al.* (2009)	UK (San Francisco)	1978-1985	Cohort	• Ex-drinker	NHL	0.60	(0.40-1.10)
					HL	0.50	(0.10-4.00)
				• Drinker, ≥3 drinks/day	NHL	0.90	(0.60-1.20)
					HL	0.70	(0.20-2.10)
Chang *et al.* (2010b)	US (California Teachers Study Cohort)	1995-2007	Cohort	• Former drinker	B-NHL	1.46	(1.08-1.97)
				• Current drinker ≥20 g/day	B-NHL	1.16	(0.82-1.65)
				• Current beer consumption	B-NHL	0.97	(0.75-1.25)
Troy *et al.* (2010)	US (PLCO)	1993-2001	Cohort	• Ever drinker ≥14 drinks/week	NHL	0.84	(0.62-1.14)
				• Beer ≥3 drinks/wk	NHL	0.89	(0.69-1.15)
				• Wine ≥3 drinks/wk	NHL	0.88	(0.69-1.12)
				• Liquor ≥3 drinks/wk	NHL	0.89	(0.69-1.16)

* Never drinkers served as reference

7.3 Characteristics of smoking and drinking behaviours

The details of the Singapore Lymphoma study have been described in **Chapter 4**. In brief, the Singapore Lymphoma Study is a hospital-based case-control study conducted in Singapore from 2004 to 2008. Lymphoma patients and hospital participants were interviewed using structured standardized questionnaire by trained research staff. Apart from basic demographics and potential confounders, extensive information about smoking and alcohol drinking was collected to evaluate its association with the risk of lymphoma in this study.

Definition of smoking status**:* Smoking status was determined by the following question: "Have you ever smoked more than 100 cigarettes in your lifetime?" Those who answered "yes" were considered as 'exposed group' and classified as "Ever smokers***". Smoking information such as the age when the subject started smoking regularly, frequency of smoking (number of cigarettes smoked in a day, number of smoking days in a week), and the age when the subject quitted smoking were collected. "***Ex-smoker***" was defined as those who stopped smoking at least 1 year prior to the date of diagnosis or interview. The reference (i.e. unexposed group) called "***Never smokers***", included subjects who did not smoke at all, or who smoked less than 100 cigarettes in their lifetime.

The quantitative smoking variables were categorized into 2 groups based on the distribution of ever smokers among the controls. Among ever smokers, we assessed the age when the subject started smoking (>17, ≤17 years), smoking intensity (1-10, >10 cig/day), smoking duration (≤17, 17-30, >30 years), and cumulative exposure in terms of pack-years (≤20, >20 pack-years). The smoking intensity in the current smokers was

further analysed separately. The years of quitting (>10, ≤10 years) was assessed in ex-smokers.

To assess the exposure to environmental tobacco smoke (ETS) (i.e. passive smoking), we also recorded information on whether household members smoked cigarettes daily at home or colleagues at work place, for at least 1 year or longer.

Definition of drinking status**:* Information on alcohol drinking is elicited from the following question: "Have you ever drunk alcohol more than once a month on average?" Those who answered "yes" were defined as "Ever drinker***", and proceeded to answer additional questions. Data collected included age when the subject started drinking (years), frequency (number of drinking days per week) and portion size at each occasion (in terms of glass, cans, small bottle, or large bottle whichever applicable) for beer, wine and hard liquor separately. Alcoholic drinking was expressed in terms of standardized portion size: one standard drink equals to a 330ml can of beer, 150ml glass of wine, or a 30ml shot of liquor. One large bottle of hard liquor equals to 17 standard drinks (NIH 2010). "***Never drinkers***" were those who did not consume or who consumed any alcoholic drink irregularly, and was used as the reference group.

Weekly alcohol consumption was determined by the total amount of alcohol consumed per week (i.e. the number of drinks on each drinking day multiplied by number of days per week), and expressed in terms of standard drinks for beer, wine and hard liquor separately. Based on the distribution of drinkers in the hospital controls, the continuous variables of alcohol consumption were categorized into 2 groups or tertiles as follow:

the age when the subject started drinking (>19, ≤19 years), the consumption of beer (<3, 3-14.9, ≥15 drinks/week), wine (<0.5, ≥0.5 drinks/week), and hard liquor (≤3, >3drinks/week). The total alcoholic consumption equals to the combined consumption of all 3 alcoholic types per week (<4, 4-39.9, >40 drinks/week). Preference of alcoholic beverage type was further divided into 7 categories (only beer, only wine, only hard liquor, beer and wine, beer and hard liquor, wine and hard liquor, all 7 types).

7.4 Statistical analysis

The distribution of smoking and drinking behaviours between males and females were compared by simple chi-square test for proportions, and Mann Whitney test if the data were skewed.

As mentioned in **Chapter 4**, an unconditional logistic regression model was used to quantify the effect of smoking or drinking on the risk of malignant lymphoma via the OR estimate and its 95%CI. In addition to potential cofounders such as age, gender, and ethnicity, we further considered adult BMI (continuous), Diabetes Mellitus status (yes/no), and vegetables and fruits consumption (in 4 categories) in the current analysis. The additional potential confounder of smoking status (Never / quitter / current smoker) was included in the alcohol consumption model; likewise drinking status (yes/no) was added in the smoking model. For other potential confounders such as marital status and country of birth, they did not change the risk estimates by over 10% and hence were not included in the respective final models.

7.5 Results

Smoking and drinking characteristics by gender

Table 7.3 summarized the characteristics of smoking and drinking behaviours by gender. In this study population, 829 controls and 532 cases answered questions on smoking behaviours. There were 62.6% and 12.9% of ever smokers in males and females respectively, and close to half of them had quitted smoking for at least a year. On average both gender started smoking at about 17 years old. As compared with female subjects, the median duration of smoking were doubled in males (12.5 years in females and 27 years in males). The smoking intensity was tripled (5 cigarette/day in females and 16 cigarette/day in males). 57.1% of females were exposed to environmental tobacco smoke at home or workplace, as compared to 43.3% in males.

In terms of drinking habit, 45% of men and 12.5% of women were regular drinkers, and both gender started drinking at 20 years old. Beer was the most commonly consumed beverages (8.0 drinks/week in males and 1.0 drink/week in females), and wine was the least common beverage with an average consumption of 0.5-0.6 drinks/week in this study population. In terms of total alcohol consumption per week, the male subjects were consuming close to 7 times as much as females (14.0 drinks/week in males and 1.8 drinks/week in females).

Table 7.3 Characteristics of smoking and drinking variables by gender.

	Males		Females		*p*-value
CIGARETTE SMOKING					
Never smokers, *n (%)*	300	(37.4%)	487	(87.1%)	
Ever smokers, *n (%)*	502	(62.6%)	72	(12.9%)	<0.001
Ex-smokers, *n (%)*	219	(27.3%)	38	(6.8%)	<0.001
Current smokers, *n (%)*	283	(35.3%)	34	(6.1%)	<0.001
Ever smokers					
Current age (years)*	53	(42 – 66)	44.5	(28.5 – 66)	0.006
Age start smoking (years)*	17	(15 – 20)	17.5	(15 – 25)	0.043
Years of smoking up to 1 year ago (years)*	27	(16 – 37)	12.5	(5 – 27.5)	<0.001
Intensity (cigarette/day)*	16	(8 – 20)	5.0	(1.7 – 10)	<0.001
Cumulative dose (pack-years)*	18	(6.3 – 38.4)	2.5	(0.3 – 10.9)	<0.001
Ex-smokers					
Current age (years)*	61	(51 – 70)	49	(40 – 70)	0.023
Years of smoking up to 1 year ago (years)*	25	(13 – 35)	9.5	(6 – 29)	0.001
Years of quitting up to 1 year ago (years)*	0	(0 – 9)	0	(0 –12.5)	0.428
Environmental tobacco smoke (ETS)					
No exposure to ETS, *n (%)*	455	(56.7%)	270	(48.3%)	0.002
Exposure to ETS, *n (%)*	347	(43.3%)	289	(51.7%)	
ALCOHOL DRINKING					
Never drinker, *n (%)*	415	(55.0%)	472	(87.6%)	
Ever drinker, *n (%)*	340	(45.0%)	67	(12.5%)	<0.001
Current age (years)*	50	(39 – 60)	41	(27 – 55)	<0.001
Age start drinking (years)*	20	(18 – 25)	20	(18 – 26)	0.339
Weekly consumption (drinks/week)*	14.0	(3.1 – 64)	1.8	(0.3 – 9.5)	<0.001
Beer (drinks/week)*	8.0	(2.5 – 24)	1.0	(0.2 – 3.0)	<0.001
Wine (drinks/week)*	0.5	(0.1 – 2.9)	0.6	(0.1 – 2.5)	0.892
Hard liquor (drinks/week)*	3.1	(0.3 – 44.5)	1.0	(0.2 – 7.7)	0.055
TOTAL	**810**		**561**		

* Median (interquartile range)

Cigarette smoking behaviour in cases and controls

In this study, 211 (39.7%) lymphoma cases (59.7% males, 12.1% females) and 363 (43.8%) hospital controls (64.4% males, 13.4% females) were ever smokers. On average, there was no difference in smoking intensity between cases and controls, with the median intensity of 15 cigarettes per day. Both started smoking at around 17 years old, but cases smoked longer than controls (29.0 years vs 24.4 years, $p<0.001$). More cases than controls quitted smoking, but this was less likely to be influenced by their illness since the time of quitting was at least 1 year prior to the date of interview.

The associations between lymphoid neoplasm and cigarette smoking are presented in **Table 7.4**. We did not observe any association between cigarette smoking behaviour with overall risk of lymphoma, regardless of the smoking status: ever smokers (OR 0.91, 95%CI 0.66-1.26), current smokers (OR 0.80, 95%CI 0.53-1.19) or ex-smokers (OR 1.01, 95%CI 0.70-1.47). Compared with never smokers, age when as subject started smoking regularly, smoking intensity and duration did not suggest any association with the risk of NHL or any subtypes. There was also no association between environmental tobacco smoke exposure and the risk of any lymphoid neoplasms. A reduced risk of HL was observed among ever smokers who smoked ≤25 years, had low intensity smoking (less than 10 cigarettes/day), and who had smoked less than 20 pack-years.

Since the smoking habit differed greatly by gender, we further assessed the interaction effect between smoking status and gender. However, no difference was observed between the males and females in the risk of any lymphoma subtypes.

Table 7.4 Estimates of OR and 95% CI for association between cigarette smoking and lymphoma

Smoking variables	Ctrl		Lymphoid neoplasms				Non-Hodgkin lymphoma				Hodgkin lymphoma			
	No	(%)	No	(%)	OR[a]	(95% CI)	No	(%)	OR[a]	(95% CI)	No	(%)	OR[a]	(95% CI)
Never smoker	466	(56.2)	321	(60.3)	1.00	(ref)	273	(59.7)	1.00	(ref)	48	(65.8)	1.00	(ref)
Ever smoker	363	(43.8)	211	(39.7)	0.91	(0.66-1.26)	184	(40.3)	1.00	(0.71-1.41)	25	(34.3)	0.52	(0.25-1.07)
Duration														
≤ 25 years	191	(23.1)	90	(16.9)	0.85	(0.58-1.25)	76	(16.6)	1.02	(0.68-1.54)	12	(16.4)	0.28	(0.11-0.73)**
>25 years	171	(20.7)	116	(21.8)	0.96	(0.64-1.43)	103	(22.5)	0.94	(0.62-1.43)	13	(17.8)	1.10	(0.45-2.66)
Intensity														
1-10 cig/day	164	(19.8)	100	(18.8)	0.91	(0.62-1.33)	90	(19.7)	1.10	(0.73-1.64)	8	(11.0)	0.28	(0.10-0.78)*
>10 cig/day	199	(24.0)	110	(20.7)	0.91	(0.62-1.34)	93	(20.4)	0.90	(0.59-1.36)	17	(23.3)	0.85	(0.37-1.96)
Cumulative Dose														
≤20 pack-years	217	(26.2)	110	(20.7)	0.85	(0.59-1.22)	96	(21.0)	1.02	(0.69-1.50)	12	(16.4)	0.27	(0.11-0.70)**
>20 pack-years	145	(17.5)	96	(18.0)	1.00	(0.65-1.51)	83	(18.2)	0.92	(0.59-1.45)	13	(17.8)	1.35	(0.54-3.34)
Age start smoking														
>17 years	202	(24.4)	101	(19.0)	0.76	(0.51-1.11)	87	(19.0)	0.82	(0.54-1.24)	12	(16.4)	0.41	(0.17-0.99)
≤17 years	160	(19.3)	105	(19.7)	1.07	(0.73-1.56)	92	(20.1)	1.17	(0.78-1.75)	13	(17.8)	0.67	(0.29-1.56)
Current smokers only	215	(25.9)	102	(19.2)	0.80	(0.53-1.19)	85	(18.6)	0.85	(0.55-1.32)	17	(23.3)	0.54	(0.23-1.24)
Intensity														
1-10 cig/day	98	(11.8)	44	(8.3)	0.72	(0.42-1.23)	38	(8.3)	0.84	(0.47-1.50)	6	(8.2)	0.37	(0.11-1.22)
>10 cig/day	117	(14.1)	57	(10.7)	0.86	(0.53-1.42)	46	(10.1)	0.84	(0.48-1.44)	11	(15.1)	0.92	(0.34-2.45)

Abbreviation: * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Numbers did not add up to 829 controls and 532 LN cases due to missing data.

[a] OR, odds ratio adjusted for age (continuous), gender (male / female), ethnicity (Chinese/Malay/Indian), education (never/<6/7-10/>10yrs), current housing types (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no), vegetable & fruits consumption (4 categories), drinking status (yes/no) and Diabetes Mellitus (yes/no) in multiple logistic regression model.

Table 7.4 (cont.)

Smoking variables	Ctrl		Lymphoid neoplasms			Non-Hodgkin lymphoma			Hodgkin lymphoma			
	No	(%)	No	(%)	OR[a] (95% CI)	No	(%)	OR[a] (95% CI)	No	(%)	OR[a]	(95% CI)
Never smoker	466	(56.2)	321	(60.3)	1.00 (ref)	273	(59.7)	1.00 (ref)	48	(65.8)	1.00	(ref)
Ex-smokers only	148	(17.9)	109	(20.5)	1.01 (0.70-1.47)	99	(21.7)	1.11 (0.75-1.65)	8	(11.0)	0.49	(0.19-1.30)
Years of quitting												
Quit >10 years	74	(8.9)	57	(10.7)	0.89 (0.55-1.45)	54	(11.8)	0.95 (0.58-1.56)	2	(2.7)	0.54	(0.11-2.58)
Quit ≤10 years	63	(7.6)	41	(7.7)	1.06 (0.62-1.80)	36	(7.9)	1.19 (0.68-2.07)	5	(6.8)	0.54	(0.14-2.02)
Environmental Tobacco Smoke (ETS)												
No ETS exposure	307	(37.0)	214	(40.3)	1.00 (ref)	182	(39.9)	1.00 (ref)	32	(43.8)	1.00	(ref)
Exposed to ETS	522	(63.0)	317	(59.7)	0.84 (0.65-1.10)	274	(60.1)	0.91 (0.69-1.22)	41	(56.2)	0.61	(0.35-1.07)

Abbreviation: * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Numbers did not add up to 830 controls and 541 LN cases due to missing data.

a OR, odds ratio adjusted for age (continuous), gender (male / female), ethnic (Chinese/Malay/Indian), education (never/<6/7-10/>10yrs), current housing types (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no), vegetable & fruits consumption (4 categories), drinking status (yes/no) and Diabetes Mellitus (yes/no) in multiple logistic regression model.

Alcoholic drinking behaviour in cases and controls

Table 7.5 shows the association of alcohol consumption and the risk of lymphoma. The alcohol-related questions were included in the SLS questionnaire in February 2005, therefore only 801 controls and 492 cases answered questions on alcohol consumption. 35.7% of hospital controls (n=286) and 24.6% of lymphoma patients (n=121) reported drinking alcohol regularly at least once a month. Among ever drinkers in Singapore, beer was the most common alcoholic beverage and was consumed by ~90% of participants (88.5% controls, 90.1% cases). Hard liquor was consumed by 69.6% of controls (n=199) and 60.3% cases (n=73). Wine was the least common beverage consumed by 40% of participants only (109 controls and 53 cases).

Compared with never drinkers, ever drinkers reported a reduced risk of lymphoid neoplasms (OR 0.71, 95%CI 0.51-0.98) and NHL (OR 0.68, 95%CI 0.48-0.96). Among those who started drinking above 19 years of age, the NHL risk was halved (OR 0.47, 95%CI 0.28-0.78). Participants who reported over 40 standard drinks per week experienced ~50% decrease in risk of NHL (95%CI 0.27-0.93). However, we did not detect any association between alcoholic beverages and HL.

In terms of alcoholic beverage types, we detected a reduced NHL risk in subjects who consumed all 3 types of beverages, i.e. beer, hard liquor and wine (OR 0.48, 95%CI 0.27-0.85) (**Table 7.5**). We further investigated the individual effect of alcoholic beverage, with additional adjustment for consumption of other alcoholic drinks; no association with any alcoholic drink was detected with the risk of lymphoma (**Table 7.6**).

Table 7.5 Estimates of OR and 95% CI for association between alcohol drinking and lymphoma

Drinking variables	Control		Lymphoid neoplasms				Non-Hodgkin lymphoma				Hodgkin lymphoma			
	No	(%)	No	(%)	OR[a]	(95% CI)	No	(%)	OR[a]	(95% CI)	No	(%)	OR[a]	(95% CI)
Never drinker	515	(64.3)	371	(75.4)	1.00	(ref)	325	(76.5)	1.00	(ref)	45	(68.2)	1.00	(ref)
Drinker	286	(35.7)	121	(24.6)	**0.71**	**(0.51-0.98)***	100	(23.5)	**0.68**	**(0.48-0.97)***	21	(31.8)	0.98	(0.49-1.93)
Age start drinking														
> 19 years	143	(17.9)	41	(8.3)	**0.51**	**(0.33-0.82)****	31	(7.3)	**0.47**	**(0.28-0.79)****	10	(15.2)	0.81	(0.33-1.96)
≤ 19 years	139	(17.4)	76	(15.4)	0.84	(0.57-1.23)	67	(15.8)	0.82	(0.55-1.24)	9	(13.6)	1.07	(0.46-2.46)
Weekly consumption														
<4 drink/week	95	(11.9)	41	(8.3)	0.75	(0.47-1.18)	34	(8.0)	0.72	(0.44-1.19)	7	(10.6)	1.03	(0.41-2.54)
4 – 39.9 drink/week	96	(12.0)	47	(9.6)	0.76	(0.49-1.18)	40	(9.4)	0.77	(0.48-1.23)	7	(10.6)	0.87	(0.33-2.29)
≥ 40 drink/week	94	(11.7)	33	(6.7)	0.60	(0.35-1.04)	26	(6.1)	**0.50**	**(0.27-0.93)***	7	(10.6)	1.10	(0.38-3.18)
Alcoholic types														
All 3 types	81	(10.1)	29	(5.9)	**0.48**	**(0.28-0.82)****	25	(5.9)	**0.48**	**(0.27-0.85)***	4	(6.1)	0.67	(0.22-2.05)
Beer + hard liquor	92	(11.5)	36	(7.3)	0.76	(0.45-1.26)	27	(6.4)	0.66	(0.37-1.16)	9	(13.6)	1.34	(0.48-3.69)
Only beer	69	(8.6)	28	(5.7)	0.61	(0.34-1.08)	25	(5.9)	0.59	(0.32-1.09)	3	(4.5)	0.84	(0.23-3.05)
Only hard liquor	16	(2.0)	4	(0.8)	0.67	(0.21-2.19)	3	(0.7)	0.66	(0.17-2.56)	1	(1.5)	0.82	(0.10-6.83)
Beer + wine	11	(1.4)	16	(3.3)	2.19	(0.92-5.23)	13	(3.1)	2.14	(0.83-5.51)	3	(4.5)	2.90	(0.71-11.87)
Wine + hard liquor	10	(1.2)	4	(0.8)	1.13	(0.33-3.91)	3	(0.7)	1.25	(0.31-5.07)	1	(1.5)	0.93	(0.11-7.98)
Only wine	7	(0.9)	4	(0.8)	0.79	(0.20-3.14)	4	(0.9)	1.01	(0.24-4.13)	0	(0.0)	-	-

Abbreviation: OR: odds ratio; CI: confidence intervals; * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Numbers did not add up to 801 controls and 492 LN cases due to missing data.

[a] OR adjusted for age (continuous), gender (male / female), ethnicity (Chinese/Malay/Indian), education (never/<6/7-10/>10yrs), current housing types (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no), vegetable and fruits consumption (4 categories), smoker status (never/quitter/smoker), and Diabetes Mellitus (yes/no) in multiple logistic regression model.

Table 7.6 Estimates of OR and 95%CI for association between alcoholic beverage types and lymphoma

Beverage types	Control		Lymphoid neoplasms			non-Hodgkin lymphoma			Hodgkin lymphoma			
	No	(%)	No	(%)	OR[a] (95% CI)	No	(%)	OR[a] (95% CI)	No	(%)	OR[a]	(95% CI)
Never drinker	515	(64.3)	371	(75.4)	1.00 (ref)	325	(76.5)	1.00	45	(68.2)	1.00	
Drinker	286	(35.7)	121	(24.6)	**0.71 (0.51-0.98)***	100	(23.5)	**0.68 (0.48-0.97)***	21	(31.8)	0.98	(0.49-1.93)
Beer drinker [1]	253	(31.6)	109	(22.2)	0.85 (0.51-1.41)	90	(21.2)	0.80 (0.46-1.38)	19	(28.8)	1.29	(0.45-3.66)
< 3 drink/week	91	(11.4)	42	(8.5)	0.90 (0.50-1.62)	32	(7.5)	0.82 (0.43-1.56)	10	(15.1)	1.52	(0.49-4.74)
3 – 14.9 drink/week	77	(9.6)	34	(6.9)	0.90 (0.48-1.70)	28	(6.6)	0.85 (0.43-1.69)	6	(9.1)	1.26	(0.34-4.71)
≥ 15 drink/week	84	(10.5)	33	(6.7)	0.74 (0.37-1.46)	30	(7.1)	0.74 (0.36-1.54)	3	(4.5)	0.81	(0.17-3.97)
Hard Liquor drinker [2]	199	(24.8)	73	(14.8)	0.93 (0.38-2.28)	58	(13.6)	0.92 (0.33-2.56)	15	(22.7)	1.02	(0.19-5.35)
≤ 3 drink/week	100	(12.5)	41	(8.3)	1.09 (0.42-2.84)	33	(7.8)	1.08 (0.37-3.17)	8	(12.1)	1.34	(0.22-8.03)
> 3 drink/week	99	(12.4)	31	(6.3)	0.76 (0.29-2.00)	24	(5.6)	0.74 (0.25-2.22)	7	(10.6)	0.83	(0.14-4.81)
Wine drinker [3]	109	(13.6)	53	(10.8)	1.65 (0.57-4.80)	45	(10.6)	1.78 (0.58-5.43)	8	(12.1)	0.94	(0.09-9.26)
< 0.5 drink/week	55	(6.9)	24	(4.9)	1.45 (0.46-4.57)	21	(4.9)	1.65 (0.50-5.48)	3	(4.5)	0.78	(0.07-8.09)
≥ 0.5 drink/week	53	(6.6)	29	(5.9)	2.15 (0.67-6.91)	24	(5.6)	2.21 (0.65-7.55)	5	(7.6)	1.97	(0.15-26.6)

Abbreviation: OR: odds ratio; CI: confidence intervals; * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Numbers did not add up to 801 controls and 492 LN cases due to missing data.

[a] OR adjusted for age (continuous), gender (male/female), ethnicity (Chinese/Malay/Indian), education (never/<6/7-10/>10yrs), current housing types (Public housing ≤3rooms/Public housing >3rooms/Private housing/Others), BMI (continuous) and history of any cancer in the first degree relatives (yes/no), vegetable & fruits consumption (4 categories), smoker status (never/quitter/smoker) and Diabetes Mellitus (yes/no) in multiple logistic regression model.

[1] Model with additional adjustment for consumption of wine (never / ever) and hard liquor (never / ever)

[2] Model with additional adjustment for consumption of beer (never / ever) and wine (never / ever)

[3] Model with additional adjustment for consumption of beer (never / ever) and hard liquor (never / ever)

7.6 Discussions

In this hospital-based case-control study, we found no association between cigarette smoking and NHL subtypes, but a decreased HL risk among those who smoked ≤20 pack-years, however this could be due to small sample size resulting in chance difference. On the other hand, a protective effect of alcohol on the risk of lymphoma was suggested. Both results showed no interactions between gender and alcohol or cigarette smoking.

Association between cigarette smoking and the risk of lymphoma

Our results did not support the association between cigarette smoking and the overall risk of lymphoid neoplasms, in terms of smoking status (ever smokers, ex-smokers or current smokers), pattern of smoking (active smoking, second hand smoking in environmental tobacco smoke), intensity, frequency or dose (pack-years). This is consistent with previous studies such as the European case-control (Besson *et al.* 2006b) and cohort (Nieters *et al.* 2008) studies, Connecticut case-control study (Morton *et al.* 2003a), and Swedish cohort studies on construction workers (Fernberg *et al.* 2006). However several case-control and cohort studies reported an increased NHL risk. The large-scaled InterLymph study reported a 7% increase in NHL risk among ever smokers (OR 1.07, 95% CI 1.00-1.15) (Morton *et al.* 2005a). Other studies only detected elevated risk in the follicular lymphoma subtype (Besson *et al.* 2003; Freedman *et al.* 1998; Herrinton & Friedman 1998; Morton *et al.* 2005a; Morton *et al.* 2003a).

Follicular lymphoma is a common indolent subtype in West, but not very common in Singapore. Chromosomal translocation t(14;18) is a characteristic of follicular lymphoma. But this may also be found in some other non-Hodgkin lymphomas, or detected in a small amount of peripheral blood lymphocytes in normal healthy people (Rabkin *et al.* 2008; Schuler *et al.* 2003). The prevalence of t(14;18) in Asians healthy individuals are lower than in Caucasians, and the frequency increased with age and smoking intensity as in pack-years (Schuler *et al.* 2003). As mentioned earlier, nicotine, tar, carcinogens and numerous hazardous additives are components in cigarettes. Exposure to dioxin or pesticides may cause t(14;18) clonal expansion, and these can also be found in cigarettes (Baccarelli *et al.* 2006; Muto & Takizawa 1989). Most of the cases we recruited in the Singapore Lymphoma Study are the aggressive subtypes, particularly Diffuse Large B-cell Lymphoma. Chang *et al* (2010a) reported a study using fluorescence in situ hybridization (FISH) to identify common translocations in NHL, t(14;18) was identified in 84% of follicular lymphoma but only 39% of DLBCL. Thus it may explain why we lack the statistical power to detect smoking-related associations in our study, possibly due to the small sample size of follicular lymphoma in our sample population.

The different associations observed across study populations may be due to various smoking intensities. From the literature, positive associations with NHL were observed in those with long duration or high intensity of smoking habits, and had increased pack-years of smoking (Freedman *et al.* 1998; Morton *et al.* 2005a). Comparing smoking intensities among ever smokers, only 7.4% controls and 5.5% cases in US Selected Cancer Studies smoked less than 0.5 packs per day (i.e. 10 cigarettes/day), and they reported a 45% increased NHL risk among those who smoked more than 2.5 packs per day (i.e. 50 cigarettes/day) (Freedman *et al.* 1998). In the pooled InterLymph study, 34.6%

controls and 32.2% NHL cases smoked with less than 10 cigarettes per day, and there was a 19% increase in risk of NHL amongst those who smoked 21-30 cigarettes/day. However in our study, 45.2% controls and 47.4% lymphoma cases smoked 10 or less cigarettes/day, or a median of 15 cigarettes per day. When comparing with other study populations, close to half of our study populations were "light smokers". It is possible that we did not have enough sample size for those who smoked "heavy" enough, in terms of daily intensity or pack-years, to show the association with NHL.

Association between alcohol drinking and the risk of lymphoma

In terms of alcohol drinking, 50.2% of males and 14.7% females of hospital controls reported being ever drinkers in our study. The National Health Surveillance Survey conducted on general population in 2007 showed 36.4% males and 14.2% females reported being ever drinkers (MOH 2009). We acknowledged that the use of hospital-based controls may have recruited patients admitted to hospital with drinking-related disease, thus may overestimating the level of drinking in the control group. Excessive alcohol drinking is associated with an increased risk of type 2 diabetes via development of insulin resistance, and obesity with truncal adiposity, which in turn is also a strong factor for Diabetes Mellitus (Howard *et al.* 2004). We have tested by removing patients admitted for Diabetes Mellitus and related chronic diseases (n=66) and repeated the analysis, but the results remained largely the same as we have presented in this chapter earlier.

In our study, compared with subjects who did not drink, results of decreased NHL risk among drinkers were consistent with the InterLymph

consortium (OR 0.83, 95%CI 0.76-0.89) (Morton *et al.* 2005b), US cohort study of >120,000 adults (≥3 drinks/day: OR 0.6, 95%CI 0.4-0.9, p-trend=0.004) (Klatsky *et al.* 2009), and UK Million Women Study (≥15 drinks/week: RR0.77, 95%CI 0.62-0.94, p-trend=0.001) (Allen *et al.* 2009). Other studies did not support any association with alcohol drinking (Benedetti *et al.* 2009; Deandrea *et al.* 2007; Kanda *et al.* 2009; Nieters *et al.* 2006; Polesel *et al.* 2007; Tavani *et al.* 2001; Troy *et al.* 2010; Willett *et al.* 2004). Several studies reported decreased NHL risk related only to wine consumption, but not with beer, spirits or hard liquor (Briggs *et al.* 2002b; Morton *et al.* 2003b). However, our results did not find any difference between beverage types, which is consistent with most of the other studies (Gorini *et al.* 2007; Morton *et al.* 2005b; Nieters *et al.* 2006; Tavani *et al.* 2001; Troy *et al.* 2010), suggesting exposure to alcohol may be reason for the decrease in risk estimates.

Alcohol has also been classified by IARC as Group 1 carcinogenic to human (IARC), and it has been positively related to many cancers, including liver cancer and other cancers along the gastrointestinal tract (Parry *et al.* 2011). The possible reasons to explain for the protective effects of alcoholic drinking against lymphoma may be related to the improved immunocompetence by low to moderate alcohol intake (Diaz *et al.* 2002), or due to the presence of antioxidants which protects against cell damage, and increased insulin sensitivity (Kato *et al.* 2003). Polyphenolic compounds presented in wine were suggested as the additional protective reasons. Among the polyphenols, the presence of resveratrol from red wine, has anti-inflammatory and antioxidant effects, inhibits metabolic activation of carcinogens, and induce apoptosis (Bianchini & Vainio 2003). However, we did not detect any risk reduction in minority local wine drinkers.

In conclusion, up to now, our data do not support a casual association with cigarette smoking in this Asian population. This could be explained by the light-smoking pattern in the Singapore population, as oppose to the elevated risk reported in the heavy-smoking populations. It is also possible that we may not have enough Follicular lymphoma accumulated in our Singapore Lymphoma Study database, we might observe a different conclusion if more cases are ascertained in this study. On the other hand, our results have suggested an inverse association between alcoholic consumption and risk of non-Hodgkin lymphoma, but not in Hodgkin lymphoma. The association did not vary with the choice of alcoholic beverages, indicating the possible effects by the alcohol in the immune system. We are mindful the drinking behaviour reflects for the period of life when "they drink regularly", our results did not suggest these are lifelong continuous drinking patterns. Further studies are needed to clarify the potential links between alcohol drinking and the lymphomagenesis.

7.7 Strength and limitations of smoking and drinking analysis

The strength of our current analysis is that the assessment of smoking characteristics in questionnaire is well established and validated in many studies. No *a priori* knowledge on the association between smoking and drinking with lymphoma was publicly known in the general population. Most people may understand their association with lung/gastrointestinal tract-related cancers, but not with lymphoma. The observed difference in risk estimates in this study population was unlikely due to differential reporting in smoking and drinking behaviour.

Secondly, we consider 1 year prior to the diagnosis of lymphoma or date of interview in hospitals as the cut-off point for defining smoking status, either as current smoker or ex-smoker. Since the hospital controls were admitted for acute medical problems only, it is unlikely for participants to report a biased smoking status due to the current illness or treatments received. We acknowledged that it is possible for lymphoma patients to quit smoking due to the disease symptoms. However, we have a mixed of aggressive (>50%) and indolent types of lymphoma in our study population, and the progression of aggressive lymphoma is usually fast, within weeks or months only. As for the slow-growing nature of indolent lymphoma, they may be undetectable for a long period of time. It is possible the cases quit smoking at their own will, long before the symptoms appear as a result of the progression of lymphoma.

We are mindful that other limitations exist in our study. Smoking and drinking are considered as addictive behaviours but it may change over time. The assumption made in this study is that the behaviour was consistent throughout the assessment period, unless the duration is specified specifically.

Comparing our results with the National Health Surveillance Survey (NHHS) at 2007, which involving >7000 respondents aged 18 to 69 years from the general population, smoking behaviour was much prevalent in hospital controls than general population, i.e. 64.4% hospital controls vs. 23.7% daily smoker in general population in males, and 13.4% vs. 3.7% in females. However, the reported smoking intensity from our study population was similar to NHHS 2007. The average cigarette smoked per day was 13 cigarettes/day and 9 cigarettes/day in males and females respectively (MOH 2009). Similarly, more hospital controls than general population in males are at least occasional drinkers (i.e. ≥ 3 drinks per month) (50.2% vs. 36.4%), but it is the same in

females (14.7% vs. 14.2%). The results suggested our controls recruited in hospitals may be associated with smoking- or drinking-related diagnosis. In a case-control study design, we assessed the exposure retrospectively. We are aware the possibilities of Berkson's bias in hospital-based settings, we have tried our best to tackle it by spreading out the admission conditions as diverse as possible, with none of the diagnosis was more than 10% of total number of admission diagnosis. The hospital controls were recruited based on their admission diagnosis but not on exposure levels.

Secondly, most of the hospital-based case-control studies did not find any associations with cigarette smoking (Besson *et al.* 2006b; De Stefani *et al.* 1998; Monnereau *et al.* 2008; Talamini *et al.* 2005), but the positive associations were reported in many population-based case-control studies (Freedman *et al.* 1998; Morton *et al.* 2005a). Considering the reason above, cigarette smoking and alcohol drinking may be associated with a wide variety of medical conditions, e.g cardiovascular diseases, and hence increased the chances of admission. Thus it may obscure the true association behind towards null. However, the elevated risk of lymphoma with smoking behaviour was detected in some cohort studies (Herrinton & Friedman 1998; Linet *et al.* 1992; Nieters *et al.* 2008) only but not all (Fernberg *et al.* 2006; Troy *et al.* 2010).

Due to the complexity of lymphoma subtypes, we did not know the potential induction period of aetiology factors on the lymphogenesis. While we could adjust for possible confounders, there will be other factors that we may not have information on. Since Diabetes Mellitus may be a confounder between alcohol drinking and lymphoma, we have tested our hypothesis by adjustment of DM status, or removing these controls from being included in the study pool. Yet both ways showed the same results as we have presented in here.

Furthermore, with regards to drinking behaviour, we have only collected information on age when the subject started drinking regularly; there was no information on the duration of drinking, or when the subject quitted drinking. Thus, we could not differentiate the drinking pattern between a continuous routine from a habit in the past. We might also have collected the behaviour at the high end of exposure, and assuming this was representative of all periods in life, as long as it was more than once a month as in our definition of drinking behaviour.

Chapter 8

Thesis summary

8.1 Current knowledge of lymphoma

In the past 170 years, there has been a lot of breakthrough in medicine. From the discovery of a rare disease by Thomas Hodgkin in 1832, till now we have a diverse group of lymphoid neoplasms (LN). The complexity of lymphoma increases by the year, with the help of advanced technology on imaging techniques, such as CT/MRI or PET scan; other important techniques including immunostaining, FISH and molecular testing to help establishing the correct diagnosis of the disease. Lymphoid neoplasms comprise many different subtypes, and all developed from a single lymphocyte. At each stage along the maturation of lymphocyte, it was triggered by different risk factors and manifested into different subtype of LN, each presented with different aggressiveness and at different target organ. The correct classification and characterization of lymphoma is so important for the suitable regimen to be given during treatment, and result in enhancing the survival rate of patients.

Many countries established national cancer registry to keep record of all cancer incidence, since then many papers have been published on the lymphoma trends changes across these years. The “Cancer Incidence in Five Continents” (IARC 2010b) was first published in 1966 by the International Agency for Research on Cancer (IARC) as a reference to the international cancer incidence. Many reports from the West suggested at least 3% increase per year of non-Hodgkin lymphoma (NHL) incident rates, until it started to level

off in early 1990s in Europe (Mitterlechner *et al.* 2006; Sandin *et al.* 2006). Similarly the Hodgkin lymphoma (HL) trends was increased until 1970s and then started to decline (Adamson *et al.* 2007).

Over the years, many epidemiology studies have been conducted to explore the aetiology of lymphoma and its relation to the rise over time. However, we still have not yet understood thoroughly about this complex disease. Except for a minority of lymphoma cases which can be explained, most of the study on risk factors generated inconsistent results.

Immunodeficiency is a more established risk factor which accounted for only a minority of cases. Studies showed a strong link between immunodeficiency and lymphomagenesis, either as primary congenital disease (Filipovich *et al.* 1992), immunocompetence resulted from organ transplant procedures (Opelz & Dohler 2004), or due to acquired immune deficiency syndrome (McGinnis *et al.* 2006). Excess risk in the second lymphoid malignancies in cancer survivors can be elevated up to 18-fold after the initial lymphoma (Royle *et al.* 2011). Besides, factors suggested to be associated with increased lymphoma risk including a history of cancer in the first degree family, especially a history of haematopoietic cancer; and autoimmune diseases such as SLE or Sjogren's syndrome (Smedby *et al.* 2006; Soderberg *et al.* 2006). Other risk factors from the literature yielded inconclusive results over the years, including pesticides (Merhi *et al.* 2007) and radiation exposures (Cano & Pollan 2001), hair dyes used (Zhang *et al.* 2008), blood transfusion (Castillo *et al.* 2010), atopy (Vajdic *et al.* 2009), contacts with animal (Tranah *et al.* 2008), exposures to bacteria (Parsonnet *et al.* 1994), virus (Matsuo *et al.* 2004; Nath *et al.* 2010) or vaccinations (Bernstein & Ross 1992; Tavani *et al.* 2000), diet

(Chang *et al.* 2006; Zhang *et al.* 1999), obesity (Renehan *et al.* 2008), reproductive factors (Adami *et al.* 1997; Glaser *et al.* 2003), parental age at birth (Lu *et al.* 2010), sleeping pattern (Lahti *et al.* 2008) or even concordance in spouse who shared lifestyles (Weires *et al.* 2011).

Almost all studies conducted so far were from the West. The common limitation in most studies is the small sample size, which is the main drawback to understand the complex lymphoid neoplasms family. The ***Interlymph Consortium*** (NCI/NIH), also called the ***International Consortium of Investigators Working on Non-Hodgkin's Lymphoma Epidemiologic Studies***, is the largest consortium from 11 countries from North America and Europe. They published pooled analysis results on lifestyle and environmental risk factors and genetics analysis from 13 cases-control studies on lymphoma. They served as the index group of all case-control studies due to their large sample size. However, there were not much information contributed from Asian populations.

8.2 What we found in this thesis

Non-Hodgkin lymphoma, as traditionally called, has increased steadily across the past few decades in Singapore (NRDO 2010), while some of the Western countries already showed a slowing down or plateauing of incidence. There were several lymphoma classification systems available in the past few decades, with almost a brand new classification in every decade. Most studies used the traditional classification of NHL so as to increase comparability with other publications. The latest age-period-cohort analysis on NHL was published

by a French study group in 2010 (Viel *et al.* 2010). Although the LN classification was release by WHO in 2001 (Jaffe *et al.* 2001) and updated in 2008 (Jaffe 2009), no paper has attempted to look at the trends of lymphoid neoplasms by incorporating HL, plasma cell myeloma and lymphoid leukaemia into consideration.

The novelty of our study was to generate several models based on different classification systems. Using 40 years of data from the Singapore Cancer Registry, our APC modelling analysis provided an understanding on the trends of lymphoma incidences in Singapore. From our results, a solid upward trend of NHL was observed across the reporting periods, as well as in advancing age groups and successive birth cohorts based on our graphical presentations. The first model used traditional grouping of NHL as in all previous publications. Our results showed that a full APC model provided the best fit and all three effects - age, period and cohort - contributed to the rising trends of lymphoma in Singapore. When we re-defined lymphoma based on the WHO classification of “B-cell neoplasms” and “T-/NK-cell neoplasms”, in addition to plasma cell myeloma and lymphoid leukaemia, similar result was observed. The full APC model showed the smallest deviance with all variables achieving statistical significance and no over-dispersion of residual found. When the novel model of LN was tested, the period effect did not improve the fit of the model after adjusting for age, gender and cohort effect. Thus our results supported that after considering HL into LN, the period effect is lost.

HL has long been considered as a separate entity of lymphoma. Not only in terms of aetiology behind, the target age group of patients, presentation of disease, regimen given for treatment, and survival rate were different from

NHL. However, HL and NHL now belongs to the same lymphoid neoplasms family under the WHO classification. The new entity "the B-cell neoplasm, cannot differentiate between DLBCL and classical Hodgkin lymphoma" in updated version provided clues to the possibility of misclassification between NHL and HL in the past. Previous studies explained that the period effect in NHL trends was due to a change in classification, which affects all age groups at a particular calendar time. Thus our results explained the period effect observed in the model using solely NHL as in previous studies, and why it disappeared in the LN model.

Our results also supported that the age and cohort effect have a strong impact on the changes in incidence of lymphoma over time. It has been suggested that a change in lifestyle or environmental exposure was responsible for the increasing incidence of lymphoma. We have then conducted a first hospital-based multi-ethnic case-control study in Singapore, which is the first in Asian countries, to explore the potential lifestyle factors, including occupations, sun exposure, smoking and drinking habits.

The Singapore Lymphoma Study was conducted in the public hospitals and national referral centres for skin and cancer between 2004 and 2008. We recruited 830 hospital controls and 541 incident cases who were age 18 years and above. The response rates of cases and controls were 89.7% and 62.4% respectively. The data was collected using standardized questionnaire through face-to-face interview by trained research nurses.

The analysis on common occupations in Singapore showed an elevated risk of NHL among the teaching professionals with ≤10 years, regardless of the

levels of teaching. It has been suggested in the literature that exposure to virus due to person-to-person contact in a large group of students may be the reason for the lymphomagenesis (Boffetta & de Vocht 2007). No association was detected in machine operators, business professionals or those working in the agricultural industry. This could be due to a lack of statistical power to detect, in a limited small sample size with mixed occupations under broad occupational category.

Singapore is a tropical country with efficient UV radiation throughout the year (WHO), as a perfect candidate to examine the association between sun exposure and the risk of lymphoma. We found that intermittent recreational sun exposure in childhood and adulthood were inversely associated with the risk of developing NHL, and it is consistent with the growing evidence across various populations. However, we did not detect any association between NHL and occupational sun exposure. Compare to their childhood, adult subjects spent much less time under the sun. It was also reflected by low sun burn frequency and few subjects using sun protection. The protective effect of sun exposure was observed to be more profound in females than males. The underlying beneficial mechanisms suggested from other studies were the role of vitamin D generated on the skin upon UV radiation. This is an important public health message addressed to the public. While most of the public campaign addresses the issue of protection against UV to avoid skin cancer in this tropical country, sun avoidance may result in low serum vitamin level which may lead to other medical problems.

A higher rate of lymphoma has been reported in males than females across countries (Ferlay *et al.* 2010). Generally speaking, there are behavioural

differences between the genders with regards to smoking and drinking habits. For this reason we have examined the association between alcohol drinking and cigarette smoking and the risk of lymphoma. Our results showed alcohol drinker, regardless of beverages types, reduced the risk of NHL. Cigarette smoking did not support the associations with NHL at all in this study population. We did not detect any other significant differences in risk estimates in smoking and drinking behaviours between genders.

8.3 The strength and limitations of current studies

In the first study of APC modelling, the lymphoma data source was from a very well-documented national cancer registry with high coverage, since the beginning of the registry in 1968. We generated several models based on the different international standard classifications used in the past few decades. The strength in this study is our reliable data source, regardless of the severity of disease or method of diagnosis, and the duration of 40 years is long enough to detect any changes in trends. APC modelling is a standard approach to investigate the independent effects of age, period and cohort, and it has been tested on many cancers in previous publications. The novelty of this study is the parallel comparison of different classifications of lymphoma which was not reported in anywhere before. We acknowledge that we may have missed some very rare subtypes which were classified under LN during the request of data, however, these subtypes usually have very few incidences, and thus should not have a significant impact on the total sample size and the subsequent APC analysis. Due to the complexity of lymphoma, our 40 years of data is not large

enough to have adequate statistical power to detect differences at subtype levels.

The Singapore Lymphoma Study is the first multi-ethnic hospital-based case-control study in Asia. The strengths of our study are that the data were collected using standardized questionnaires, and with reference to a prestige study group in Europe. The multi-centre design covered the majority of public facilities in Singapore, and both cases and controls were referred to hospitals under similar referral pattern, hence we have accessed to a representative sample of eligible incident cases and controls in this country. The case-control study is an effective design for studying the exposures retrospectively within a short period.

At the same time, we are mindful of the limitations. We attempted to remove the interviewer bias (since we cannot blind the interviewers regarding the participants' disease states) by standardizing all interviews according the standard operating procedures. Besides, the interviewers were requested to interview both cases and controls. We may have missed some important information from the advanced stage patients since they were too sick to be interviewed. Low participation from hospital controls may introduce selection bias. We have made an effort to reduce this by recruiting only patients with acute diagnosis, and with wide coverage on admission reasons, so as to minimize the risk of biased selection of hospital controls who may have over-exposed to certain risk factors. We hope through these procedures we would minimize the confounding factors which we may not be able to control for. The retrospective nature of case-control study design may have a recall bias. No established association between any known factors, regardless of occupational

exposure, sun exposure, smoking and drinking, and the risk of lymphoma is well-known in the general population. The observed difference in risk estimates in this study population was unlikely due to differential reporting in these behaviour we evaluated in the thesis.

8.4 Proposed future studies

Further studies on lifestyle factors and medical history are needed to study their association with the risk of lymphoma in this Asian population. From the literature, we know that altered immune function, or immunosuppression, was a known reason for the increased risk of lymphoma. It is possible that lymphoma risk also reflects the subtle change in immune system responses which was sharpened by childhood exposure to virus or bacteria (Bufford & Gern 2005). Thus the term "hygiene hypothesis" was first proposed by Dr David Strachan in 1989, suggesting a relationship between atopy, family size and birth order (Strachan 1989). In particular, the following risk factors may be of interest:

Sibship size and birth order: It has been postulated that the risk of lymphoma may be related to delayed exposure to infection during childhood. Absence of exposures to infections may lead to an immune system skewed towards T-helper 2 (Th2) type of immune response instead of Th1. A Danish population cohort study reported that the risk of HL decreases with increasing sibship size (RR 0.91, 95%CI 0.81-1.03) and birth order (RR 0.85, 95%CI 0.71-1.01) in young adults over 15 years of age (Westergaard *et al.* 1997). However, the association was not supported by other studies,

which suggested it was a biased due to low SES effect (Grulich *et al.* 2010; Mensah *et al.* 2007)

Atopy: Atopy is a predisposition towards developing allergic hypersensitivity to environmental allergens, and characterized by an immune-response that is skewed toward a Th2-dominant response (Grulich *et al.* 2007a). Previous studies suggested a reduced NHL risk is associated with a history of atopy due to immune dysregulation. In the analysis of 13 case-control studies in InterLymph, asthma and hay fever was associated with 10% and 20% reduction in NHL risk respectively (Vajdic *et al.* 2009).

Autoimmune disease: Systematic autoimmune disease may increase the risk of lymphoma due to its association with Th1 dominated immune response. SLE, psoriasis and rheumatoid arthritis have a higher risk of developing NHL and HL (Ekstrom Smedby *et al.* 2008; Smitten *et al.* 2008; Soderberg *et al.* 2006). Other studies reported null association (Smedby *et al.* 2006; Tavani *et al.* 2000).

Hepatitis B / C virus (HBV/HCV): Infectious virus will induce chronic immune stimulation and persistently activate lymphocytes (Engels 2007). HCV infection is strongly associated with benign B-cell lymphoproliferative disorder (Charles & Dustin 2009). In a meta-analysis of 23 studies, HCV infection was associated with close to 6-fold increased NHL risk (Matsuo *et al.* 2004). Similarly, HBV is a common hepatotrophic and lymphotrophic virus. In studies involving countries where hepatitis infection is endemic, those who were hepatitis B service antigen (HBsAg) seropositive had a relative risk for NHL ranging from 1.7 to 4.1 fold, as compared with those

with HBsAg sero-negative (Engels *et al.* 2010; Fwu *et al.* 2011; Nath *et al.* 2010).

Type 2 diabetes mellitus (DM): Type 2 DM is associated with altered immune function. In two independent meta-analysis of diabetes with NHL, a moderately elevated (~20%) risk was reported (Chao & Page 2008; Mitri *et al.* 2008).

Blood transfusion: Due to the immunogenic effects of red blood cells, allogeneic transfusions have been suggested as a risk factor for development of lymphoma. In a meta-analysis of 9 case-control and 5 cohort studies, the relative risk of developing NHL was 1.2 (95%CI 1.07-1.35) in those who had received allogeneic transfusions (Castillo *et al.* 2010).

Further, it has long been speculated that common polymorphic variation contributed to the susceptibility of cancers. No definite susceptibility alleles have been identified so far. With the advanced molecular technique, genome-wide association study (GWAS) is a powerful approach for identification of common, low-penetrance loci without a priori knowledge about the function. We can then incorporate the genetic profile, with the lifestyle factors collected by the traditional epidemiological studies, to investigate the link between them. From previous studies in the West on GWAS or genotyping analysis, the followings are the areas suggested to be associated with lymphoma in inflammatory or immune-related systems, and hence these are some suggestions for future work in the Asian populations:

Proinflammatory cytokine gene: A study on the polymorphisms in immune system-related genes, tumour necrosis factor (TNF) and interleukin-10 (IL-10), was associated with NHL risk as reported by InterLymph based on 7,999 NHL cases and 8,452 controls (Skibola *et al.* 2010). A 3-folded increase in NHL risk was observed in TNF polymorphism in the Chinese study (Zhang *et al.* 2012).

Human Leukocyte antigen (HLA): People with a history of autoimmune disease have increased risk of NHL. GWAS studies showed the single nucleotide polymorphisms (SNPs) at the HLA class II region (chromosome 6p21.32) were significantly associated with nodular sclerosis HL (Cozen *et al.* 2012) and follicular lymphoma (Conde *et al.* 2011). The same region was possibly sharing genetic aetiology with DLBCL subtypes as suggested by the Swedish study (Smedby *et al.* 2011).

Cytokine polymorphism: Chen *et al* (2011) reported a case-control study on common genetic variation in Th1 and Th2 cytokine genes. Connecticut women with BMI ≥25kg/m^2 had elevated NHL risk in those who carried IFNGR2 AA, IL5 CT/TT, IL7R AA and TNF CC genotype.

Interleukin 2 (IL2) gene: IL2 plays an important role in proliferation of T- and NK-cell. Song *et al* (2012) examine the effects of polymorphism of IL2 with the risk of NHL in China. The prevalence of -330G/+114T haplotype was associated with NHL (OR 1.45, 95% CI 1.12-1.88).

In conclusion, as the first multi-ethnic lymphoma study in Asia, our results have contributed to a missing piece in the bigger puzzle. With the findings collected from traditional epidemiology studies over the years across the world, and the new knowledge at molecular level by the genome-wide studies, our future directions entail a new melting pot to put these information together, and taking one big step ahead to unveil the truth behind and advance our knowledge.

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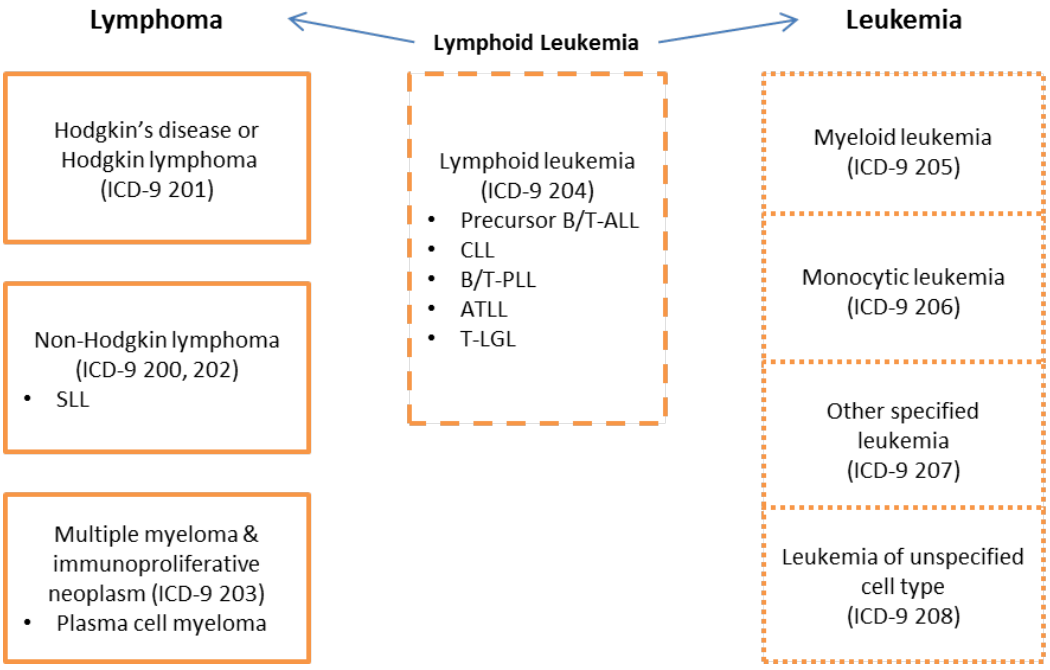
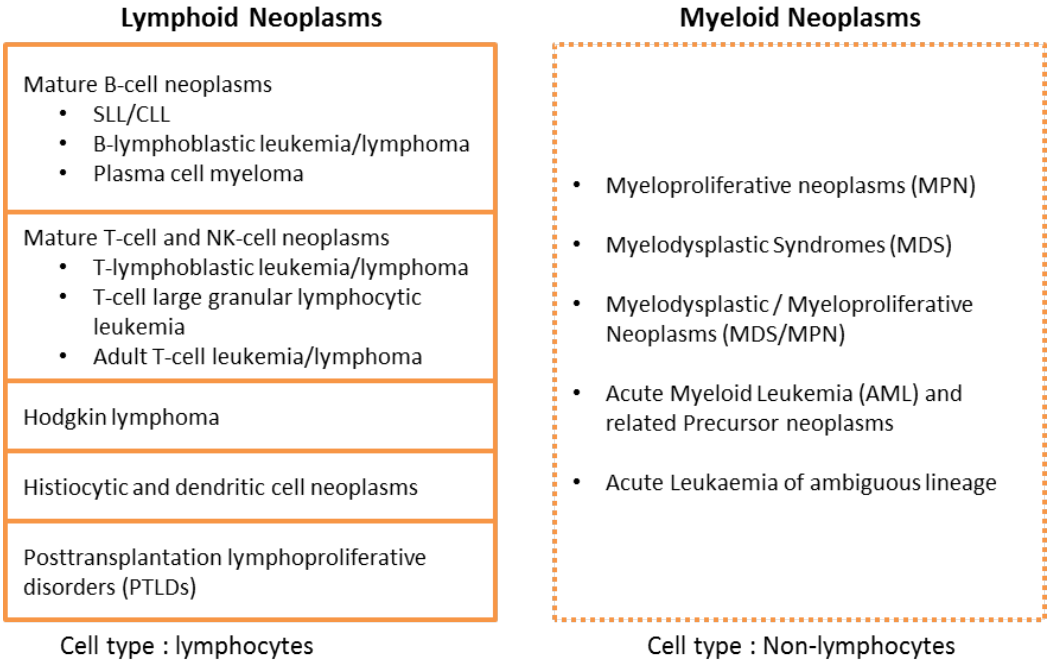
Appendix 1 - Schematic diagrams of changes in classification of lymphoma and leukaemia

Traditional understanding of haematopoietic malignancies:



WHO classification 4th Edition (2008) (Swerdlow *et al.* 2008) :



Appendix 2 – International Classification of Diseases (ICD) for lymphatic and haematopoietic diseases [1]

ICD, Revision 6 (1948)

(200-205) Neoplasms of lymphatic and haematopoietic tissues
- 200 Lymphosarcoma and reticulosarcoma
- 201 Hodgkin's disease
- 202 Other forms of lymphoma (reticulosis)
- 203 Multiple myeloma (plasmocytoma)
- 204 Leukaemia and aleukaemia
- 205 Mycosis fungoides

ICD, Revision 7 (1955)

(200-207) Neoplasms of lymphatic and haematopoietic tissues
- 200 Lymphosarcoma and reticulosarcoma
- 201 Hodgkin's disease
- 202 Other forms of lymphoma (reticulosis)
- 203 Multiple myeloma (plasmocytoma)
- 204 Leukaemia and aleukaemia
- 205 Mycosis fungoides
- 206 Lymphatic system
- 207 Haematopoietic system

ICD, Revision 8 (1965)

(200-209) Neoplasms of lymphatic and haematopoietic tissue
- 200 Lymphosarcoma and reticulum-cell sarcoma
- 201 Hodgkin's disease
- 202 Other neoplasms of lymphoid tissue
- 203 Multiple myeloma
- 204 Lymphatic leukaemia
- 205 Myeloid leukaemia
- 206 Monocytic leukaemia
- 207 Other and unspecified leukaemia
- 208 Polycythaemia vera
- 209 Myelofibrosis

ICD, Revision 9 (1975)

(200-208) Malignant neoplasm of lymphatic and haematopoietic tissue
- 200 Lymphosarcoma and reticulosarcoma
- 201 Hodgkin's disease
- 202 Other malignant neoplasm of lymphoid and histiocytic tissue
- 203 Multiple myeloma and immunoproliferative neoplasms
- 204 Lymphoid leukaemia
- 205 Myeloid leukaemia
- 206 Monocytic leukaemia
- 207 Other specified leukaemia
- 208 Leukaemia of unspecified cell type

ICD, Revision 10 (1990)

(C81-C96) Malignant neoplasm of lymphoid, haematopoietic and related tissue
- C81 Hodgkin's disease
- C82 Follicular [nodular] non-Hodgkin's lymphoma
- C83 Diffuse non-Hodgkin's lymphoma
- C84 Peripheral and cutaneous T-cell lymphomas
- C85 Other and unspecified types of non-Hodgkin's lymphoma
- C88 Malignant immunoproliferative diseases
- C90 Multiple myeloma and malignant plasma cell neoplasms
- C91 Lymphoid leukaemia
- C92 Myeloid leukaemia
- C93 Monocytic leukaemia
- C94 Other leukaemias of specified cell type
- C95 Leukaemia of unspecified cell type
- C96 Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue

[1] *International Classification of Diseases. Available from http://www.wolfbane.com/icd/index.html (last update on 7 April 2007), accessed in 2011.*

Appendix 3 – International Classification of Diseases for Oncology: Morphology of Neoplasms (ICD-O) for lymphatic and haematopoietic systems [1]

ICD-O, Edition 1 (1975)

(M959-M963) Lymphomas, NOS or diffuse

- M9590/0 Lymphomatous tumour, benign
- M9590/3 Malignant lymphoma NOS
- M9591/3 Malignant lymphoma, non-Hodgkin's type
- M9600/3 Malignant lymphoma, undifferentiated cell type NOS
- M9601/3 Malignant lymphoma, stem cell type
- M9602/3 Malignant lymphoma, convoluted cell type NOS
- M9610/3 Lymphosarcoma NOS
- M9611/3 Malignant lymphoma, lymphoplasmacytoid type
- M9612/3 Malignant lymphoma, immunoblastic type
- M9613/3 Malignant lymphoma, mixed lymphocytic-histiocytic NOS
- M9614/3 Malignant lymphoma, centroblastic-centrocytic, diffuse
- M9615/3 Malignant lymphoma, follicular centre cell NOS
- M9620/3 Malignant lymphoma, lymphocytic, well differentiated NOS
- M9621/3 Malignant lymphoma, lymphocytic, intermediate differentiation NOS
- M9622/3 Malignant lymphoma, centrocytic
- M9623/3 Malignant lymphoma, follicular centre cell, cleaved NOS
- M9630/3 Malignant lymphoma, lymphocytic, poorly differentiated NOS
- M9631/3 Prolymphocytic lymphosarcoma
- M9632/3 Malignant lymphoma, centroblastic type NOS
- M9633/3 Malignant lymphoma, follicular centre cell, noncleaved NOS

(M964-M964) Reticulosarcomas

- M9640/3 Reticulosarcoma NOS
- M9641/3 Reticulosarcoma, pleomorphic cell type
- M9642/3 Reticulosarcoma, nodular

(M965-M966) Hodgkin's disease

- M9650/3 Hodgkin's disease NOS
- M9651/3 Hodgkin's disease, lymphocytic predominance
- M9652/3 Hodgkin's disease, mixed cellularity
- M9653/3 Hodgkin's disease, lymphocytic depletion NOS
- M9654/3 Hodgkin's disease, lymphocytic depletion, diffuse fibrosis
- M9655/3 Hodgkin's disease, lymphocytic depletion, reticular type
- M9656/3 Hodgkin's disease, nodular sclerosis NOS
- M9657/3 Hodgkin's disease, nodular sclerosis, cellular phase
- M9660/3 Hodgkin's paragranuloma
- M9661/3 Hodgkin's granuloma
- M9662/3 Hodgkin's sarcoma

(M969-M969) Lymphomas, nodular or follicular

- M9690/3 Malignant lymphoma, nodular NOS
- M9691/3 Malignant lymphoma, mixed lymphocytic-histiocytic, nodular
- M9692/3 Malignant lymphoma, centroblastic-centrocytic, follicular
- M9693/3 Malignant lymphoma, lymphocytic, well differentiated, nodular
- M9694/3 Malignant lymphoma, lymphocytic, intermediate differentiation, nodular
- M9695/3 Malignant lymphoma, follicular centre cell, cleaved, follicular
- M9696/3 Malignant lymphoma, lymphocytic, poorly differentiated, nodular
- M9697/3 Malignant lymphoma, centroblastic type, follicular
- M9698/3 Malignant lymphoma, follicular centre cell, noncleaved, follicular

[1] *International Classification of Diseases. Available from http://www.wolfbane.com/icd/index.html (last update on 7 April 2007), accessed in 2011.*

(M970-M970) Mycosis fungoides
- M9700/3 Mycosis fungoides
- M9701/3 Sézary's disease

(M971-M972) Miscellaneous reticuloendothelial neoplasms
- M9710/3 Microglioma
- M9720/3 Malignant histiocytosis
- M9721/3 Histiocytic medullary reticulosis
- M9722/3 Letterer-Siwe's disease

(M973-M973) Plasma cell tumours
- M9730/3 Plasma cell myeloma
- M9731/0 Plasma cell tumour, benign
- M9731/1 Plasmacytoma NOS
- M9731/3 Plasma cell tumour, malignant

(M974-M974) Mast cell tumours
- M9740/1 Mastocytoma NOS
- M9740/3 Mast cell sarcoma
- M9741/3 Malignant mastocytosis

(M975-M975) Burkitt's tumour
- M9750/3 Burkitt's tumour

(M980-M980) Leukaemias NOS
- M9800/3 Leukaemia NOS
- M9801/3 Acute leukaemia NOS
- M9802/3 Subacute leukaemia NOS
- M9803/3 Chronic leukaemia NOS
- M9804/3 Aleukaemic leukaemia NOS

(M981-M981) Compound leukaemias
- M9810/3 Compound leukaemia

(M982-M982) Lymphoid leukaemias
- M9820/3 Lymphoid leukaemia NOS
- M9821/3 Acute lymphoid leukaemia
- M9822/3 Subacute lymphoid leukaemia
- M9823/3 Chronic lymphoid leukaemia
- M9824/3 Aleukaemic lymphoid leukaemia
- M9825/3 Prolymphocytic leukaemia

(M983-M983) Plasma cell leukaemias
- M9830/3 Plasma cell leukaemia

(M984-M984) Erythroleukaemias
- M9840/3 Erythroleukaemia
- M9841/3 Acute erythraemia
- M9842/3 Chronic erythraemia

(M985-M985) Lymphosarcoma cell leukaemias
- M9850/3 Lymphosarcoma cell leukaemia

(M986-M986) Myeloid leukaemias
- M9860/3 Myeloid leukaemia NOS
- M9861/3 Acute myeloid leukaemia
- M9862/3 Subacute myeloid leukaemia
- M9863/3 Chronic myeloid leukaemia
- M9864/3 Aleukaemic myeloid leukaemia
- M9865/3 Neutrophilic leukaemia
- M9866/3 Acute promyelocytic leukaemia

(M987-M987) Basophilic leukaemias
- M9870/3 Basophilic leukaemia

(M988-M988) Eosinophilic leukaemias
- M9880/3 Eosinophilic leukaemia

(M989-M989) Monocytic leukaemias
- M9890/3 Monocytic leukaemia NOS
- M9891/3 Acute monocytic leukaemia
- M9892/3 Subacute monocytic leukaemia
- M9893/3 Chronic monocytic leukaemia
- M9894/3 Aleukaemic monocytic leukaemia

(M990-M994) Miscellaneous leukaemias
- M9900/3 Mast cell leukaemia
- M9910/3 Megakaryocytic leukaemia
- M9920/3 Megakaryocytic myelosis
- M9930/3 Myeloid sarcoma
- M9940/3 Hairy cell leukaemia

(M995-M997) Miscellaneous myeloproliferative and lymphoproliferative disorders
- M9950/1 Polycythaemia vera
- M9951/1 Acute panmyelosis
- M9960/1 Chronic myeloproliferative disease
- M9961/1 Myelosclerosis with myeloid metaplasia
- M9962/1 Idiopathic thrombocythaemia
- M9970/1 Chronic lymphoproliferative disease

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(M965-M966) Hodgkin's disease

M9650/3 Hodgkin's disease NOS
M9652/3 Hodgkin's disease, mixed cellularity NOS
M9653/3 Hodgkin's disease, lymphocytic depletion NOS
M9654/3 Hodgkin's disease, lymphocytic depletion, diffuse fibrosis
M9655/3 Hodgkin's disease, lymphocytic depletion, reticular
M9657/3 Hodgkin's disease, lymphocytic predominance NOS
M9658/3 Hodgkin's disease, lymphocytic predominance, diffuse
M9659/3 Hodgkin's disease, lymphocytic predominance, nodular
M9660/3 Hodgkin's paragranuloma NOS
M9661/3 Hodgkin's granuloma
M9662/3 Hodgkin's sarcoma
M9663/3 Hodgkin's disease, nodular sclerosis NOS
M9664/3 Hodgkin's disease, nodular sclerosis, cellular phase
M9665/3 Hodgkin's disease, nodular sclerosis, lymphocytic predominance
M9666/3 Hodgkin's disease, nodular sclerosis, mixed cellularity
M9667/3 Hodgkin's disease, nodular sclerosis, lymphocytic depletion

(M967-M968) Malignant lymphoma, diffuse or NOS, specified type

M9670/3 Malignant lymphoma, small lymphocytic NOS
M9671/3 Malignant lymphoma, lymphoplasmacytic
M9672/3 Malignant lymphoma, small cleaved cell, diffuse
M9673/3 Malignant lymphoma, lymphocytic, intermediate differentiation, diffuse
M9674/3 Malignant lymphoma, centrocytic
M9675/3 Malignant lymphoma, mixed small and large cell, diffuse
M9676/3 Malignant lymphoma, centroblastic-centrocytic, diffuse
M9677/3 Malignant lymphomamatous polyposis
M9680/3 Malignant lymphoma, large cell, diffuse NOS
M9681/3 Malignant lymphoma, large cell, cleaved, diffuse
M9682/3 Malignant lymphoma, large cell, noncleaved, diffuse
M9683/3 Malignant lymphoma, centroblastic, diffuse
M9684/3 Malignant lymphoma, immunoblastic NOS
M9685/3 Malignant lymphoma, lymphoblastic
M9686/3 Malignant lymphoma, small cell, noncleaved, diffuse
M9687/3 Burkitt's lymphoma NOS

(M969-M969) Malignant lymphoma, follicular or nodular, with or without diffuse areas

M9690/3 Malignant lymphoma, follicular NOS
M9691/3 Malignant lymphoma, mixed small cleaved and large cell, follicular
M9692/3 Malignant lymphoma, centroblastic-centrocytic, follicular
M9693/3 Malignant lymphoma, lymphocytic, well differentiated, nodular
M9694/3 Malignant lymphoma, lymphocytic, intermediate differentiation, nodular
M9695/3 Malignant lymphoma, small cleaved cell, follicular
M9696/3 Malignant lymphoma, lymphocytic, poorly differentiated, nodular
M9697/3 Malignant lymphoma, centroblastic, follicular
M9698/3 Malignant lymphoma, large cell, follicular NOS

(M970-M970) Specified cutaneous and peripheral T-cell lymphomas
- M9700/3 Mycosis fungoides
- M9701/3 Sézary's disease
- M9702/3 Peripheral T-cell lymphoma NOS
- M9703/3 T-zone lymphoma
- M9704/3 Lymphoepithelioid lymphoma
- M9705/3 Peripheral T-cell lymphoma, AILD (angioimmunoblastic lymphadenopathy with dysproteinaemia)
- M9706/3 Peripheral T-cell lymphoma, pleomorphic small cell
- M9707/3 Peripheral T-cell lymphoma, pleomorphic medium and large cell
- M9709/3 Cutaneous lymphoma

(M971-M971) Other specified non-Hodgkin's lymphomas
- M9711/3 Monocytoid B-cell lymphoma
- M9712/3 Angioendotheliomatosis
- M9713/3 Angiocentric T-cell lymphoma
- M9714/3 Large cell (Ki-1+) lymphoma

(M972-M972) Other lymphoreticular neoplasms
- M9720/3 Malignant histiocytosis
- M9722/3 Letterer-Siwe disease
- M9723/3 True histiocytic lymphoma

(M973-M973) Plasma cell tumours
- M9731/3 Plasmacytoma NOS
- M9732/3 Multiple myeloma

(M974-M974) Mast cell tumours
- M9740/1 Mastocytoma NOS
- M9740/3 Mast cell sarcoma
- M9741/3 Malignant mastocytosis

(M976-M976) Immunoproliferative diseases
- M9760/3 Immunoproliferative disease NOS
- M9761/3 Waldenström's macroglobulinaemia
- M9762/3 Alpha heavy chain disease
- M9763/3 Gamma heavy chain disease
- M9764/3 Immunoproliferative small intestinal disease
- M9765/1 Monoclonal gammopathy
- M9766/1 Angiocentric immunoproliferative lesion
- M9767/1 Angioimmunoblastic lymphadenopathy
- M9768/1 T-gamma lymphoproliferative disease

(M980-M980) Leukaemias NOS
- M9800/3 Leukaemia NOS
- M9801/3 Acute leukaemia NOS
- M9802/3 Subacute leukaemia NOS
- M9803/3 Chronic leukaemia NOS
- M9804/3 Aleukaemic leukaemia NOS

(M982-M982) Lymphoid leukaemias
- M9820/3 Lymphoid leukaemia NOS
- M9821/3 Acute lymphoblastic leukaemia NOS
- M9822/3 Subacute lymphoid leukaemia
- M9823/3 Chronic lymphocytic leukaemia
- M9824/3 Aleukaemic lymphoid leukaemia
- M9825/3 Prolymphocytic leukaemia
- M9826/3 Burkitt's cell leukaemia
- M9827/3 Adult T-cell leukaemia/lymphoma

(M983-M983) Plasma cell leukaemia
- M9830/3 Plasma cell leukaemia

(M984-M984) Erythroleukaemias
- M9840/3 Erythroleukaemia
- M9841/3 Acute erythraemia
- M9842/3 Chronic erythraemia

(M985-M985) Lymphosarcoma cell leukaemia
- M9850/3 Lymphosarcoma cell leukaemia

(M986-M986) Myeloid (granulocytic) leukaemias
- M9860/3 Myeloid leukaemia NOS
- M9861/3 Acute myeloid leukaemia
- M9862/3 Subacute myeloid leukaemia
- M9863/3 Chronic myeloid leukaemia
- M9864/3 Aleukaemic myeloid leukaemia
- M9866/3 Acute promyelocytic leukaemia
- M9867/3 Acute myelomonocytic leukaemia

M9868/3 Chronic myelomonocytic leukaemia

(M987-M987) Basophilic leukaemia

M9870/3 Basophilic leukaemia

(M988-M988) Eosinophilic leukaemia

M9880/3 Eosinophilic leukaemia

(M989-M989) Monocytic leukaemias

M9890/3 Monocytic leukaemia NOS
M9891/3 Acute monocytic leukaemia
M9892/3 Subacute monocytic leukaemia
M9893/3 Chronic monocytic leukaemia
M9894/3 Aleukaemic monocytic leukaemia

(M990-M994) Other leukaemias

M9900/3 Mast cell leukaemia
M9910/3 Acute megakaryoblastic leukaemia
M9930/3 Myeloid sarcoma
M9931/3 Acute panmyelosis
M9932/3 Acute myelofibrosis
M9940/3 Hairy cell leukaemia
M9941/3 Leukaemic reticuloendotheliosis

(M995-M997) Miscellaneous myeloproliferative and lymphoproliferative disorders

M9950/1 Polycythaemia vera
M9960/1 Chronic myeloproliferative disease
M9961/1 Myelosclerosis with myeloid metaplasia
M9962/1 Idiopathic thrombocythaemia
M9970/1 Lymphoproliferative disease

(M998-M998) Myelodysplastic syndrome

M9980/1 Refractory anaemia NOS
M9981/1 Refractory anaemia without sideroblasts
M9982/1 Refractory anaemia with sideroblasts
M9983/1 Refractory anaemia with excess of blasts
M9984/1 Refractory anaemia with excess of blasts with transformation
M9989/1 Myelodysplastic syndrome NOS

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(M959-M959) Malignant lymphomas, NOS or diffuse

M9590/3 Malignant lymphoma, NOS
M9591/3 Malignant lymphoma, non-Hodgkin's, NOS
M9596/3 Composite Hodgkin's and non-Hodgkin's lymphoma

(M965-M966) Hodgkin's lymphoma

M9650/3 Hodgkin's lymphoma, NOS
M9651/3 Hodgkin's lymphoma, lymphocyte-rich
M9652/3 Hodgkin's lymphoma, mixed cellularity, NOS
M9653/3 Hodgkin's lymphoma, lymphocyte depletion, NOS
M9654/3 Hodgkin's lymphoma, lymphocyte depletion, diffuse fibrosis
M9655/3 Hodgkin's lymphoma, lymphocyte depletion, reticular
M9659/3 Hodgkin's lymphoma, nodular lymphocyte predominance
M9661/3 Hodgkin's granuloma (obs)
M9662/3 Hodgkin's sarcoma (obs)
M9663/3 Hodgkin's lymphoma, nodular sclerosis, NOS
M9664/3 Hodgkin's lymphoma, nodular sclerosis, cellular phase
M9665/3 Hodgkin's lymphoma, nodular sclerosis, grade 1
M9667/3 Hodgkin's lymphoma, nodular sclerosis, grade 2

(M967-M969) Mature B-cell lymphomas

- M9670/3 Malignant lymphoma, small B lymphocytic, NOS (see also M9823/3)
- M9671/3 Malignant lymphoma, lymphoplasmacytic (see also M9761/3)
- M9673/3 Mantle cell lymphoma
- M9675/3 Malignant lymphoma, mixed small and large cell, diffuse (obs) (see also M9690/3)
- M9678/3 Primary effusion lymphoma
- M9679/3 Mediastinal large B-cell lymphoma (C38.3)
- M9680/3 Malignant lymphoma, large B-cell, diffuse, NOS
- M9684/3 Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS
- M9687/3 Burkitt's lymphoma, NOS (see also M9826/3)
- M9689/3 Splenic marginal B-zone lymphoma (C42.2)
- M9690/3 Follicular lymphoma, NOS (see also M9675/3)
- M9691/3 Follicular lymphoma, grade 2
- M9695/3 Follicular lymphoma, grade 1
- M9698/3 Follicular lymphoma, grade 3
- M9699/3 Marginal zone B-cell lymphoma, NOS

(M970-M971) Mature T- and NK-cell lymphomas

- M9700/3 Mycosis fungoides (C44._)
- M9701/3 Sézary's syndrome
- M9702/3 Mature T-cell lymphoma, NOS
- M9705/3 Angioimmunoblastic T-cell lymphoma
- M9708/3 Subcutaneous panniculitis-like T-cell lymphoma
- M9709/3 Cutaneous T-cell lymphoma, NOS (C44._)
- M9714/3 Anaplastic large cell lymphoma, T-cell and Null cell type
- M9716/3 Hepatosplenic gamma-delta cell lymphoma
- M9717/3 Intestinal T-cell lymphoma
- M9718/3 Primary cutaneous CD30+ T-cell lymphoproliferative disorder (C44._)
- M9719/3 NK/T-cell lymphoma, nasal and nasal-type

(M972-M972) Precursor cell lymphoblastic lymphoma

- M9727/3 Precursor cell lymphoblastic lymphoma, NOS (see also M9835/3)
- M9728/3 Precursor B-cell lymphoblastic lymphoma (see also M9836/3)
- M9729/3 Precursor T-cell lymphoblastic lymphoma (see also M9837/3)

(M973-M973) Plasma cell tumours

- M9731/3 Plasmacytoma, NOS
- M9732/3 Multiple myeloma (C42.1)
- M9733/3 Plasma cell leukaemia (C42.1)
- M9734/3 Plasmacytoma, extramedullary (not occurring in bone)

(M974-M974) Mast cell tumours

- M9740/1 Mastocytoma, NOS
- M9740/3 Mast cell sarcoma
- M9741/3 Malignant mastocytosis
- M9742/3 Mast cell leukaemia (C42.1)

(M975-M975) Neoplasms of histiocytes and accessory lymphoid cells

- M9750/3 Malignant histiocytosis
- M9751/1 Langerhans cell histiocytosis, NOS
- M9752/1 Langerhans cell histiocytosis, unifocal
- M9753/1 Langerhans cell histiocytosis, multifocal
- M9754/3 Langerhans cell histiocytosis, disseminated
- M9755/3 Histiocytic sarcoma
- M9756/3 Langerhans cell sarcoma
- M9757/3 Interdigitating dendritic cell sarcoma
- M9758/3 Follicular dendritic cell sarcoma

(M976-M976) Immunoproliferative diseases

- M9760/3 Immunoproliferative disease, NOS

M9761/3 Waldenström's macroglobulinaemia (C42.0) (see also M9671/3)
M9762/3 Heavy chain disease, NOS
M9764/3 Immunoproliferative small intestinal disease (C17._)
M9765/1 Monoclonal gammopathy of undetermined significance
M9766/1 Angiocentric immunoproliferative lesion
M9767/1 Angioimmunoblastic lymphadenopathy
M9768/1 T-gamma lymphoproliferative disease
M9769/1 Immunoglobulin deposition disease

(M980-M980) Leukaemias, NOS (C42.1)
M9800/3 Leukaemia, NOS
M9801/3 Acute leukaemia, NOS
M9805/3 Acute biphenotypic leukaemia

(M982-M983) Lymphoid leukaemias (C42.1)
M9820/3 Lymphoid leukaemia, NOS
M9823/3 B-cell chronic leukaemia / small lymphocytic lymphoma (see also M9670/3)
M9826/3 Burkitt's cell leukaemia (see also M9687/3)
M9827/3 Adult T-cell leukaemia/lymphoma (HTLV-1 positive)
M9831/1 T-cell large granular lymphocytic leukaemia
M9832/3 Prolymphocytic leukaemia, NOS
M9833/3 Prolymphocytic leukaemia, B-cell type
M9834/3 Prolymphocytic leukaemia, T-cell type
M9835/3 Precursor cell lymphoblastic leukaemia, NOS (see also M9727/3)
M9836/3 Precursor B-cell lymphoblastic leukaemia (see also M9728/3)
M9837/3 Precursor T-cell lymphoblastic leukaemia (see also M9729/3)

(M984-M993) Myeloid leukaemias (C42.1)
M9840/3 Acute myeloid leukaemia, M6 type
M9860/3 Myeloid leukaemia, NOS
M9861/3 Acute myeloid leukaemia, NOS (FAB or WHO type not specified) (see also M9930/3)
M9863/3 Chronic myeloid leukaemia, NOS
M9866/3 Acute promyelocytic leukaemia, t(15;17)(q22;q11-12)
M9867/3 Acute myelomonocytic leukaemia
M9870/3 Acute basophilic leukaemia
M9871/3 Acute myeloid leukaemia with abnormal marrow eosinophils
M9872/3 Acute myeloid leukaemia, minimal differentiation
M9873/3 Acute myeloid leukaemia without maturation
M9874/3 Acute myeloid leukaemia with maturation
M9875/3 Chronic myelogenous leukaemia, BCR/ABL positive
M9876/3 Atypical chronic myeloid leukaemia, BCR/ABL negative
M9891/3 Acute monocytic leukaemia
M9895/3 Acute myeloid leukaemia with multilineage dysplasia
M9896/3 Acute myeloid leukaemia, t(8;21)(q22;q22)
M9897/3 Acute myeloid leukaemia, 11q23 abnormalities
M9910/3 Acute megakaryoblastic leukaemia
M9920/3 Therapy-related acute myeloid leukaemia, NOS
M9930/3 Myeloid sarcoma (see also M9861/3)
M9931/3 Acute panmyelosis with myelofibrosis (C42.1)

(M994-M994) Other leukaemias (C42.1)
M9940/3 Hairy cell leukaemia (C42.1)
M9945/3 Chronic myelomonocytic leukaemia, NOS
M9946/3 Juvenile myelomonocytic leukaemia
M9948/3 Aggressive NK-cell leukaemia

(M995-M996) Chronic myeloproliferative disorders (C42.1)

M9950/3 Polycythaemia vera
M9960/3 Chronic myeloproliferative disease, NOS
M9961/3 Myelosclerosis with myeloid metaplasia
M9962/3 Essential thrombocythaemia
M9963/3 Chronic neutrophilic leukaemia
M9964/3 Hypereosinophilic syndrome

(M997-M997) Other haematological disorders

M9970/1 Lymphoproliferative disorder, NOS
M9975/1 Myeloproliferative disease, NOS

(M998-M998) Myelodysplastic syndromes (C42.1)

M9980/3 Refractory anaemia
M9982/3 Refractory anaemia with sideroblasts
M9983/3 Refractory anaemia with excess blasts
M9984/3 Refractory anaemia with excess blasts in transformation (obs)
M9985/3 Refractory cytopenia with multilineage dysplasia
M9986/3 Myelodysplastic syndrome with 5q deletion (5q-) syndrome
M9987/3 Therapy-related myelodysplastic syndrome, NOS
M9989/3 Myelodysplastic syndrome, NOS

Appendix 4 – COMMITTEE OF THE SINGAPORE LYMPHOMA STUDY

Principal investigator

A/Prof Adeline Seow	Saw Swee Hock School of Public Health, NUS

Co-investigators

A/Prof Chia Sin-Eng	Saw Swee Hock School of Public Health, NUS
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Dr Susan Loong	Dept of Radiation Oncology, NCC
Dr Wong Gee Chuan	Dept of Haematology, SGH
Dr Leonard Tan	Dept of Pathology, SGH
Dr Tan Soo Yong	Dept of Pathology, SGH
Dr Tan Suat Hoon	Dept of Dermatolgoy, NSC
Dr Ponnudurai Kuperan	Dept of Laboratory Medicine, TTSH

Participating institutes

NCC	National Cancer Centre
NUH	National University Hospital
NSC	National Skin Centre
SGH	Singapore General Hospital
TTSH	Tan Tock Seng Hospital

Appendix 5

SINGAPORE LYMPHOMA STUDY QUESTIONNAIRE (*Version 2.6b.*)

Questionnaire on Health, Genes and Environment
健康，基因 与 环境问卷调查

Serial No.: □-□□□□-□□

Content :

1	Date of interview 受访日期	☐☐ / ☐☐ / ☐☐☐☐ d d (日) m m (月) y y y y (年)
2	Name of interviewee 受访者姓名	
3	NRIC Number 身份证号码	☐-☐☐☐☐☐☐☐-☐
4	Sex 性别	☐ Male 男 ☐ Female 女
5	Date of birth 出生日期	☐☐ / ☐☐ / ☐☐☐☐ d d (日) m m (月) y y y y (年)
6	Address 居住地址	Block no. 大牌 : _____ Street name 街道名: _____ Unit no. 单位 : _____ Postal code 邮政号码 : _____

PLACE of interview ☐ NUH ☐ SGH ☐ NCC ☐ NSC ☐ TTSH

Ward / Clinic _____

For controls (tick all that apply) :

Diagnosis _____

The current admission
- ☐ Not for diagnosis or suspicion of malignancy
- ☐ Not asthma, atopic eczema or allergy
- ☐ Not for immune-related disorder (e.g. SLE, Crohn's, RA)
- ☐ Not for peptic ulcer disease
- ☐ Not for viral hepatitis or tuberculosis

In addition
- ☐ No history of organ transplantation
- ☐ Not known to be positive for HIV/AIDS

ECOG SCORE AT DIAGNOSIS (rate activity of patients / controls immediately prior to treatment)

0.	Fully active, able to carry on all pre-disease performance without restriction
1.	Restricted in physically strenuous activity but ambulatory, able to carry out light house or office work
2.	Ambulatory, able to self-care but unable to work. Up and about >50% of waking hours
3.	Capable of limited self-care, confined to bed/chair >50% of waking hours
4.	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair
9.	Unknown

INTERVIEWER Name _____ Signature _____

Serial No.: ☐-☐☐☐☐-☐☐ DOB： (M/F) Ethnic:

PART I. PERSONAL PARTICULARS / JOB HISTORY 个人及就业资料

A. Ethnic group and birth place 族裔及出生地	
1A.1	What is your Ethnic group 您的族裔 ? 1. Chinese 华裔 2. Malay 馬來裔 3. Indian 印度裔 4. Others 其它族裔
1A.2	What is your Father's Ethnic group 您父親的族裔 ? 1. Chinese 华裔 2. Malay 馬來裔 3. Indian 印度裔 4. Others 其它族裔
1A.3	What is your Mother's Ethnic group 您母親的族裔? 1. Chinese 华裔 2. Malay 馬來裔 3. Indian 印度裔 4. Others 其它族裔
1A.4	Where were you born? 您在那里出生？ 1. Singapore 新加坡 2. Malaysia 马来西亚 3. Hong Kong / Taiwan 香港 / 台湾 4. PR China 中国大陆 (Province _____ 省) 5. Other 其它(Specify 请具体说明: _____)
1A.5	If not born in Singapore, at what age did you come to live in Singapore? _____ 如果您不在新加坡出生，您几岁开始住在新加坡？ _ years old 岁
B. Siblings 兄弟姐妹 (excluded adopted and half siblings 同父异母/同母异父/领养的除外)	
1B.1	What is the order number that you are within your siblings? 您在家里排第几? _____ / Don't know
1B.2	How many brothers do you have? 您有多少个兄弟 _____ / Don't know
1B.3	How many sisters do you have? 您有多少个姐妹 _____ / Don't know
C. Marital status 婚姻状况	
1C.1	Are you ….? 您现在是? 1. never married 没有结过婚 2. currently married 目前已婚 3. separated / widowed or divorced 分居 / 丧偶 / 离异
	Question 1C.1a & b for women only :
1C.1a	Have you ever been pregnant? 您有没有曾经怀孕? 1. Yes 有 2. No 没有
1C.1b	How many children (live births) have you had? 您总共有生过几个孩子? _____
D. Housing 房屋	
1D.1	Do you currently live in….. ? 您现在住的房屋类别….. ? 1. HDB or other Govt 1-3 room flat (including shop-house) HDB /其它政府组屋 1-3 房室(包括店屋) 2. HDB 4-room flat HDB 4 房室 3. HDB 5-room flat HDB 5 房室 4. HDB executive 公寓式组屋 5. Private / HUDC apt or condominium 私人房或公寓 6. Terrace / semi-detached / bungalow 排屋 / 半独立式洋房 / 独立式洋房 7. Other 其它(Specify 请具体说明: _____)
E. Others 其他	
1E.1a	How many years have you attended school, in total? (from primary school) 您总共受了多少年的在校教育 ? _____ years 年
1E.1b	How many years have you studied in kindergarten? 您总共读了多少年的幼稚园 ? _____ years 年
1E.2	Are you currently employed? 您目前正被雇用或曾经被雇用吗? 1. Yes, currently employed (includes self-employed) 目前正受雇用(包括自我雇用) 2. No, previously employed / retired 曾受过雇用 / 退休 3. No, never employed (e.g. homemaker / students) 从来没有被雇用(例如：家庭主妇/学生)
1E.3	What is your usual adult height? 您平時的身高是多少？ _____ cm 厘米
1E.4	What is your usual adult weight? 您平時的体重是多少？ _____ kg 公斤
1E.5	Have you recently (in the past 6-12 months) lost or gained more than 5 kg of your usual adult weight? 您最近的六到十二个月内，是否比您平時的体重减轻或加重超过 5 公斤以上? 1. Yes 有 2. No 没有

F. Job History 工作记录

1F.1 Please tell us about **all the jobs you have held** starting with the first job you had after leaving general

school. Include all major job changes within the same company as separate jobs, (e.g. permanent moves to different sectors, any promotions). **Ignore jobs you held for less than 1 year** but include all periods without any job (housekeeping, apprenticeship, military service, working on family farm/ business) if they were lasting at least 1 year.

Job history without time gaps

Job #	**a. Company name (optional) 公司名稱 （选择性）**		**b. Type of Industry 行业**	**c. Occupation title 职业**
#1				
	d. Year began 开始年份	**e. Year ended 完结年份**	**f. No. of hours spending outdoor on normal working day 工作时共有多少时间留在室外**	**g. Any sun protection used?* 有没有用防晒用品？**
			Hrs/day 小时/日	1. Yes 有 2. No 没有
	h. Describe your job (what you did on a typical day, and how you did it) 请说明一下您平时的工作			
	i. What machines/equipment/chemicals did you use on a typical work day? 平时工作上，有没有用什么机器/仪器/化学用品？			

* includes broad-brimmed hat / scarf, long sleeves, sun cream; excludes sunglasses.

1F.2	**a. In the course of any of your jobs, did you handle any of the following? 任何的工作中，要不要接触以下的化学用品？**		**b. If yes, Year started 如果有，开始年份**	**c. Total no. of years 总共年期**
1F2.1	Solvents 溶劑	1. Yes 有 2. No 没有		
1F2.2	Paints 油漆	1. Yes 有 2. No 没有		
1F2.3	Paint removers 除油漆劑	1. Yes 有 2. No 没有		
1F2.4	Metal degreasing / metal cleaning agents 金属去油劑	1. Yes 有 2. No 没有		
1F2.5	Fuels 燃料	1. Yes 有 2. No 没有		
1F2.6	Ionizing radiation (e.g. X rays) 離子化輻射能	1. Yes 有 2. No 没有		
1F2.7	Pesticides 除草劑	1. Yes 有 2. No 没有		

PART II. PERSONAL MEDICAL HISTORY 个人病历

A. SELF RATING HEALTH 自我健康评估

Of the following sentences, which one(s) correctly best describe your **childhood up to the age of 10**? *(Read out each sentence)* 在下面的句子，哪些句子是比较正确的描述您小时候 **(少於 10 岁)** ?

2A.1	I was more often sick than my schoolmates were. 我比同学较多生病.	1. Yes 是 2. No 否 3. Don't know 不知道
2A.2	I was absent in the school more often than my school mates. 我比同学较多请病假.	1. Yes 是 2. No 否 3. Don't know 不知道
2A.3	I used to take more medicines than my brothers/sisters. 我比兄弟姐妹较吃更多的药.	1. Yes 是 2. No 否 3. Don't know 不知道
2A.4	I was a very healthy child. 我是非常健康的小孩.	1. Yes 是 2. No 否 3. Don't know 不知道

B. VACCINATION 预防针

2B.1	When you were a child，were you vaccinated according to the official guidelines at the time? (e.g . BCG + Tetanus + Poliomyelitis) 您小時候有没有按照规定接種疫苗？(如: 肺结核 + 破伤风 +小兒麻痹症)	1. Yes 是 2. No 否 3. Don't know 不知道
2B.2	If no, do you know the reason? 如果没有，知道原因吗？	

Apart from vaccinations listed in the official guidelines, have you ever been vaccinated for any of the followings? *(read out all diseases)* 除了规定之外，您有没有接種以下疫苗？

No. 编号	i. Disease 疾病	ii. Vaccination 接種預防疫苗	iii. Age 年齡
2B.3a	Hepatitis B 乙型肝炎	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3b	Cholera 霍乱	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3c	Small pox 天花	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3d	Yellow fever 黄热病	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3e	Typhoid fever 伤寒	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3f	Influenza 流行性感冒	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3g	Tuberculosis* 肺结核	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3h	Tetanus* 破伤风	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3i	Poliomyelitis* 小兒麻痹症	1. Yes 是 2. No 否 3. Do not remember 沒想起來	
2B.3j	Others (please specify) 其他 (请具体说明):		

*exclude if answer to 2B.1 is 'yes'

C. MEDICAL HISTORY 病历				
2C.1	Do you have any allergy? 您有沒有过敏症?		1. Yes 是 2. No 否	
2C.2	If yes, what are you allergy to ? 如果有，对什么敏感 ？	**a. Age at first time 最初年龄**	**b. Age at the last time 最后年龄**	**c. Number of episodes (in a year) 发病次数（每年）**
2C2.1	Food products 食品			
2C2.2	Drugs 药物			
2C2.3	Pollen 花粉			
2C2.4	Dust Mite 灰尘螨			
2C2.5	Milk (lactose intolerance) 奶类			
2C2.6	Animals 動物			
2C2.7	Others, please specify 其他, 请具体说明			

Have you ever been told by doctor that you had any of the following illnesses? 您以前有沒有曾经给医生诊断有以下任何病症?

No. 编号	**Disease 疾病**	**a. Diagnosis 诊断**	**b. Age at first diagnosis 初诊年龄**	**c. Need any medications? 需要服药?**
Related to the Head 头部				
2C3.1	Allergic rhinitis 鼻敏感	1. Y 是 2. N 否		
2C3.2	Sinusitis 鼻窦炎	1. Y 是 2. N 否		
2C3.3	Herpes in the lips / cold sore 疱疹一型（单纯疱疹）	1. Y 是 2. N 否		
2C3.4	Asthma 哮喘 / 气喘	1. Y 是 2. N 否		
Related to chest 胸部				
2C3.5	Tuberculosis 结核病	1. Y 是 2. N 否		
2C3.6	Myocardial infarction / Ischaemic heart disease (heart disease due to blockage in the blood vessels) 心肌梗塞 / 心绞痛	1. Y 是 2. N 否		
Related to the abdomen or pelvis 腹部				
2C3.7	Hepatitis A 甲型肝炎	1. Y 是 2. N 否		
2C3.8	Hepatitis B 乙型肝炎	1. Y 是 2. N 否		
2C3.9	Hepatitis C 丙型肝炎	1. Y 是 2. N 否		
2C3.10	Other Hepatitis 其他肝炎	1. Y 是 2. N 否		
2C3.11	Gastric ulcer / duodenal 胃溃疡 / 十二指肠的溃疡	1. Y 是 2. N 否		
2C3.12	Recurrent Diarrhoea 周期性發生的腹泻	1. Y 是 2. N 否		
2C3.13	Herpes other sites 疱疹二型（生殖器疱疹）	1. Y 是 2. N 否		

No. 编号	Disease 疾病	a.Diagnosis 诊断	b. Age at first diagnosis 初诊年龄	c. Need any medications? 需要服药?
Related to bones / joints 骨/关节				
2C3.14	Rheumatoid arthritis 类风湿性关节炎	1. Y 是 2. N 否		
2C3.15	Other arthritis (e.g. gout / non-specific arthritis) 关节炎	1. Y 是 2. N 否		
Related to the skin 皮肤				
2C3.16	Shingles 带状疱疹	1. Y 是 2. N 否		
2C3.17	Eczema (child) 湿疹 (小孩)	1. Y 是 2. N 否		
2C3.18	Eczema (adult) 湿疹 (成人)	1. Y 是 2. N 否		
2C3.19	Urticaria / Hives 荨麻疹 (风疹块)	1. Y 是 2. N 否		
Systemic conditions **系统性**				
2C3.20	Hypertension (high blood pressure) 高血压	1. Y 是 2. N 否		
2C3.21	Hypercholesterolaemia (high blood cholesterol) 高胆固醇	1. Y 是 2. N 否		
2C3.22	Systemic Lupus **Erythematosus (SLE) 系统性红斑狼疮**	1. Y 是 2. N 否		
2C3.23	Goiter 甲状腺肿	1. Y 是 2. N 否		
2C3.24	Diabetes Mellitus (high blood sugar) 糖尿病	1. Y 是 2. N 否		(for Diabetes, specify if tablets or injection)
2C3.25	Mononucleosis 传染性单核细胞增多症 (glandular fever 腺性热)	1. Y 是 2. N 否		
2C3.26	Chronic Anemia 长期贫血	1. Y 是 2. N 否		
2C3.27	Cataract 白内障	1. Y 是 2. N 否		
2C3.28	Any other disease that has not been mentioned 还有其他的吗？_____	1. Y 是 2. N 否		

2C4.1	Have you ever been told by doctor that you have a tumour or cancer? 您有否曾经诊断患上肿瘤 / 癌症 ？			1. Yes 是 2. No 否
2C4.2	If yes, please specify 如果有，请具体说明	**c. Type 類型**	**d. Age at Diagnosis 初诊年龄**	**e. To be filled by the coordinator (ICD-O)**
	a. Site of tumour 肿瘤位置 b. Hospital where it was diagnosed 就诊医院	1. Benign 良性的 2. Malignant 恶性的	Years old	C
2C4.3	If yes, do you remember if you were treated with : 如果有，您记得有否接受過以下治疗?			
	2C43.1	Radiotherapy 放射治疗		1. Yes 是 2. No 否
	2C43.2	Chemotherapy 化学治疗		1. Yes 是 2. No 否
	2C43.3	Surgery 手术治疗		1. Yes 是 2. No 否
	2C43.4	Others (please specify) 其他 (请具体说明)		

D. X-ray X 光照片

Have you ever had any of the following types of X-ray? 請您指出以下列出身體不同位置給拍過 X 光照片的。

No. 编号	Site 位置		a. No. of times 次数	b. Age first 最初年龄	c. Age last 最後年龄
2D.1	Abdomen with contrast (oral or enema) 腹部 （有用造影检查） （口服钡剂追踪或灌肠）	1. Yes 是 2. No 否			
2D.2	Kidneys with Contrast (IVU) 肾脏（有用造影检查）	1. Yes 是 2. No 否			
2D.3	Others X-ray examination on a regular basis, e.g. yearly (specify) : __ 其他（请具体说明）_____	1. Yes 是 2. No 否			

Age group 年龄组别
(Enter and CIRCLE the corresponding code if interviewee is unable to give exact age).

1. <10 yrs 少於 10 岁
2. 10-19 yrs old/岁
3. 20-29 yrs old/岁
4. 30-39 yrs old/岁
5. 40-49 yrs old/岁
6. 50-59 yrs old/岁
7. ≥60 yrs old/岁以上

E. ANTIBIOTICS 抗生素

2E.1	Have you ever taken **antibiotics** at any time in your life? 您是否曾經服用**抗生素** ？ 1. Yes 是 2. No 否
2E.2	How often, on average, did you need a course of antibiotics for an infection? (tick in the appropriate box) 平均来说，您有多少次由於感染而服用抗生素?

		Frequency 次数				
		Never 沒有	Less than once a year 一年少过一次	1-3 times per year 一年一到三次	4-6 times a year 一年四到六次	More than 6 times a year 一年超过六次
2E2.a	**Adolescence 少年时期**					
2E2.b	**21 – 40 yrs old 二十–四十岁**					
2E2.c	**Over 40 yrs old 超过四十岁**					

F. LONG TERM MEDICATION / TREATMENT 长期医药治療

2F.1	Have you ever been on any of the following treatments **at least once a day for six months or more**? 您是否曾经接受以下的医药治疗，每天至少一次，持续超過六个月以上?	1. Yes 是 2. No 否

No. 编号	TREAMENT 治疗		a.Reason 原因	Duration 服药时期		d. Total months of use 总共 (月)
				b. Age start 初诊年龄	c. Age ended* 最后年龄	
2F.2	Analgesics 止痛药 (Panadol)	1. Y 是 2. N 否				
2F.3	Analgesics 止痛药 (other NSAID)	1. Y 是 2. N 否				
2F.4	Antihypertensive drug 降高血压药	1. Y 是 2. N 否				
2F.5	Cholesterol-lowering drug 降胆固醇药	1. Y 是 2. N 否				
2F.6	Anti-TB drug 抗结核病药	1. Y 是 2. N 否				
2F.7	Oral hypoglycaemics (for diabetes) 抗糖尿药	1. Y 是 2. N 否				
2F.8	Anti-depressive drug 抗抑郁症药	1. Y 是 2. N 否				
2F.9	Steroids 類固醇類药	1. Y 是 2. N 否				
2F.10	Immunosuppressants 免疫抑制药	1. Y 是 2. N 否				
2F.11	Medication for sleep disorders 睡眠失调药	1. Y 是 2. N 否				
2F.12	Any hormones including oral contraceptives 任何类形的荷尔蒙包括口服避孕药	1. Y 是 2. N 否				
2F.13	Traditional Chinese Medicine / Malay medicine (e.g. herbal tea etc) 传统草药治疗/ 偏方 (例：中草药或马来草药)	1. Y 是 2. N 否				
2F.14	Other long-term medication (pls specify): 其他药类（请具体说明）					

*If ongoing, write current age.

G. BLOOD TRANSFUSION 捐血/输血				
2G.1	Have you ever donated blood (including rd cells, plasma or other blood derivatives)? 您有沒有曾经捐血（包括血細胞球，血浆，或其他血制品）？			1. Yes 是 2. No 否
2G.2	Have you ever received a blood transfusion (including red cells, plasma or other blood derivatives)? 您有沒有曾经接受输血（包括血細胞球，血浆，或其他血制品）？			1. Yes 是 2. No 否
2G.3	If yes, what is the reason and how old were you when this happened? 如果有，是什么原因，几岁发生 ？			
	a. Reason 原因	**b. Total no. of transfusions for this reason 总共输血次数**	**c. Age at first transfusion 开始输血年龄**	
	1.			
	2.			
	3.			

H. HOSPITALIZATION AND SURGICAL HISTORY 住院及手术资料			
2H.1	(Apart from the current admission) Have you ever admitted to hospital ? （除了这次住院）您有否曾经住进医院?		1. Yes 是 2. No 否
2H.2	If yes, do you remember whether you have ever admitted to hospital before and when was it? 如果有，您记得以前为了什么原因住院? 哪时几岁?		
	a. Reasons for Hospitalization 住院原因		**b. Age 年龄**
	1.		
	2.		
	3.		
2H.3	Have you ever been operated on ? (e.g. tonsillectomy, removal of appendix, Caesarean section, or any other form of surgery) 您有否曾经做過手术? （如咽喉扁桃腺或盲肠切除手术，剖腹生产术或任何其他的手术）		1. Yes 是 2. No 否
2H.4	Could you specify what type of operation and how old were you when this happened? 您记得做過什么手术? 哪时几岁?		
	a. Operation 手术		**b. Age 年龄**
	1.		
	2.		
	3.		

Age group 年龄组别 (Enter and CIRCLE the corresponding code if interviewee is unable to give exact age).

1. <10 yrs 少於 10 岁
2. 10-19 yrs old/岁
3. 20-29 yrs old/岁
4. 30-39 yrs old/岁
5. 40-49 yrs old/岁
6. 50-59 yrs old/岁
7. ≥60 yrs old/岁以上

PART III. LIFESTYLE 生活习惯

A RESIDENCE ABROAD 国外生活			
3A.1	Have you ever lived in **Africa** or **Latin America**, or **other parts of Asia** more than one month at a time, or more than four months in a particular year (in total)? 您有没有居住在 非洲，拉丁美洲 或其他的亚洲国家超过一个月或一年总共超过四个月？		1. Yes 有 2. No 没有
3A1.1	If yes, which countries have you lived in for more than one month at a time or more than four months in a particular year? 如果有，有住在哪个国家超过一个月或一年总共超过四个月？		
	a. Country 国家	**b. Age 年龄**	**c. Duration 期间**
	1.		
	2.		
3A.2	Each time you lived abroad, did you suffer afterwards from any disease that was related to having been in that country? 您有没有曾经因住在国外而患病?		1. Yes 有 2. No 没有
3A2.1	If yes, what was the diagnosis? 如果有，知道诊断的结果吗？		
	a. Diagnosis 诊断	**b. Code (ICD-9)**	
	1.		
	2.		

B. USUAL PHYSICAL ACTIVITY IN THE PAST YEAR 经常性体能活动

On the average, during **the past year**, how many hours in a day did you spent in the following activities, either as work or leisure? 在**过去一年**里，您平均一天做几个小时下列体能性的活动 (包括工作和娱乐) 。

No. 编号	**Types of activities 活动类别**	**hours/day 小时/天**	
		Workdays 工作日	**Weekends or rest days 休息日**
3B.1	**Vigorous Activity**: digging in the garden, strenuous sports, jogging, aerobic dancing, tennis, squash, swimming laps, bicycling on hills, heavy carpentry, moving heavy furniture, loading or unloading trucks, shoveling or equivalent manual work, etc **剧烈活动** ： 在院子挖土耕种，伸展运动，慢跑运动，韵律操，网球，壁球，游泳，骑自行车上山，重木匠活，搬运重家具，装卸货物，铲煤，或其它同等强度的日常工作.	a	e
3B.2	**Moderate Activity:** heavy housework e.g mopping floor, washing clothes with hands, hanging clothes, light sports, regular or brisk walking, golf, yard work, painting, repairing things, ballroom dancing, yoga, pilate, bicycling on level ground, bowling, tai chi, chi kung, etc. **中等强度活动** ： 繁重的家务如抹地, 手洗衣物，晾衣，轻量体育运动, 常速或快步走，高尔夫球, 亭院工作，画画，修理家什，慢节奏跳舞，在平地上骑自行车，保龄球，太极，气功.	b	f
3B.3	**Light / Sitting Activity**: leisure, light sports, light housework e.g sweeping, ironing, office work, driving car, strolling, personal care, standing with little motion, eating, reading, desk work, watching TV, listening to radio, sewing, playing cards etc. **轻量 / 座立活动** ： 轻松的家务如扫地，办公室工作，驾车，慢步，自我照顾，有轻微运动的站立，吃饭, 读书，在写字台前工作，看电视，听广播，缝纫，打牌.	c	g
3B.4	**Sleeping 睡眠**	d	h
	TOTAL	**24**	**24**

C. OUTDOOR LEISURE ACTIVITIES 室外閒暇运动

I would like you to tell me how much time you spent outdoors in different periods of your life. By definition, outdoors means being **outside between 9am to 5pm and not under any shade**.
在不同的时期，你留在室外的时间也不同。根据定义，**室外**即在**早上的九点到下午五点，在没有遮蓋的地方**。

		a. School days 学校日	b. Non-school days (weekends or holidays) 放假日
Childhood –Adolescence 小时候 - 青年期 (e.g. <20 years 少过 20 岁)			
3C.1	How many hours do you spent outdoors? *(maximum 10 hours)* 您有多少时间留在室外？（最多 10 小时）	hours 小时	hours 小时
3C.2	Did you regularly practice **outdoor leisure activities** between 9am and 5pm? (e.g. swimming / sailing / jogging / golf / tennis etc.) 您有常常在上午九点到下午五点做室外的閒暇运动？(如游泳，帆船，跑步，高尔夫球 ，网球等)	1. Yes 有 2. No 没有	1. Yes 有 2. No 没有
3C.3	Were you using any sun protection? (e.g hat / sun-cream / long sleeves etc.) 您有没有用任何防晒用品？(帽子 / 防晒露 / 長袖衣服)	1. Yes 有; (specify) 2. No 什么也没有用	1. Yes 有; (specify) 2. No 什么也没有用

		a. Working/school days 工作或学校日	b. Non-working days 空闲或放假日
Adolescence – Adult 青年期 - 成年 (e.g >=20 years 20 岁或以上)			
3C.4	How many hours do you spent outdoors? *(maximum 10 hours)* 您有多少时间留在室外？（最多 10 小时）	hours 小时	hours 小时
3C.5	Did you regularly practice **outdoor leisure activities** between 9am and 5pm? (e.g. swimming / sailing / jogging / golf / tennis etc.) 您有常常在上午九点到下午五点做室外的閒暇运动？(如游泳，帆船，跑步，高尔夫球 ，网球等)	1. Yes 有 2. No 没有	1. Yes 有 2. No 没有
3C.6	Were you using any sun protection? (e.g hat / sun-cream / long sleeves etc.) 您有没有用任何防晒用品？(帽子 / 防晒露 / 長袖衣服)	1. Yes 有; (specify) 2. No 什么也没有用	1. Yes 有; (specify) 2. No 什么也没有用

D. SKIN COLOUR AND SOLAR RADIATION 皮肤颜色与太阳辐射

3D.1	Which colour best describes the colour of your eyes? 您的眼睛是什么颜色? 1. Black / Dark brown 黑色 / 深棕色 2. Light Brown 淡褐色 3. Other 其他
3D.2	What is the colour that best describes **the colour of your skin with no suntan** (internal part of your arm)? 在没有晒黑以前，您的皮肤是什么颜色？(手臂内部的颜色) 1. Very white 非常白 2. White 白 3. Light tan 浅黄褐色 4. Tan 黄褐色 5. Dark brown 深棕色 6. Black 黑色 7. Albino 白化病 8. Other 其他
3D.3	Have you ever had sunburn? 您至今有没有给太阳晒伤? 1. Yes 有 2. No 没有 (skip to 3D.6) 3. Don't know 不知道 (skip to 3D.6)

3D.4	How old were you when you first had sunburn? 您第一次给晒伤是几岁?	_____ Y
3D.5	How often have you had sunburn in your lifetime? 您有没有给太阳晒伤? 1. None 从来没有 2. Seldom (<5 times) 很少 （<5 次） 3. Occasionally (5-10 times) 有时（5-10 次） 4. Frequently (>10 times) 常常 （>10 次）	
3D.6	What would happen to your skin if it was exposed to bright sunlight for one hour or more in the middle of the day without any protection? 暴露在全盛太阳下**超過一小时**没有保护，您的皮肤会怎么样? 1. Get severe sunburn with blistering 严重晒伤，起水泡 2. Have painful sunburn for a few days followed by peeling 痛苦的晒伤， 会脱皮 3. Get mildly burnt followed by some tanning 有一点点晒伤，有晒黑 4. Go brown without any sunburn 只有晒黑，没有晒伤	

E. USE OF HAIR DYE 使用头发染料

3E.1	How would you describe the original colour of your hair? 您會怎样形容你头发原来的颜色？ 1. Dark brown 深棕色 2. Black 黑色 3. Light brown 淺棕色 4. Blonde 金黃色 5. Red 紅色 6. Others 其他_____					
3E.2	Have you ever used hair dye or any hair colouring product? 您有没有用过头发染料？ 1. Yes 有 2. No 没有 (skip to Section F)					
3E.3	If yes, what type of dye did you use and in which period of your life? 如果有，常用的是哪一种染料？					
	a. Dye Type 染料类型	**b. Extent 程度**	**c. Colour 颜色**	**d. Age first used 最初年龄**	**e. Age last used 最後年龄**	**f. Number of applications (per yr) 次数 (每年)**
#1	1. Permanent 持久的 2. Semi-permanent 半持久的 3. Temporary 暫时的	1. Complete 完全 2. Highlight 挑染	1. Black 黑色 2. Blonde/Lt brown 金黃色 3. Dk Brown 深棕色 4. Red 紅色 5. Others 其他			
#2	1. Permanent 持久的 2. Semi-permanent 半持久的 3. Temporary 暫时的	1. Complete 完全 2. Highlight 挑染	1. Black 黑色 2. Blonde/Lt brown 金黃色 3. Dk Brown 深棕色 4. Red 紅色 5. Others 其他			
#3	1. Permanent 持久的 2. Semi-permanent 半持久的 3. Temporary 暫时的	1. Complete 完全 2. Highlight 挑染	1. Black 黑色 2. Blonde/Lt brown 金黃色 3. Dk Brown 深棕色 4. Red 紅色 5. Others 其他			

Note :

1. Temporary : products that wash out in 1 shampoo
2. Semi-permanent : products that wash out in 6-10 shampoos
3. Permanent : products that do not wash out after repeated shampoos and leave a line as they grow out

F. DIET 饮食习惯

1.) Fresh Vegetables 蔬菜品种

I would like you to think about **fresh vegetables** that you consumed either by themselves, in mixed dishes with fish or meat, or in soups **during the past year**.
请您回忆一下您在**过去一年**里无论是单独所吃，和鱼，肉类，汤类混合所吃的**蔬菜**的种类和数量。

No 编号	FRESH VEGETABLES 蔬菜品种	a. Frequency and Usual portion size 通常食用的平均次数及份量 CHOOSE ONE according to photograph 请根据相片, 填上您每次所吃的份量: **A** – Small / 小 ; **B** – Medium / 中; **C** – Large / 大								
		Never or less than once a year 一年少于一次或没有	At least once a year but less than once a month 每月少 过一次但一年 至少一次	1-3 times a month 一个月 1-3 次	Once a week 一个星期一次	2-3 times a week 一个星期 2-3 次	4-6 times a week 一个星期 4-6 次	Once a day 一天一次	2-3 times a day 一天 2-3 次	b. SIZE 份量
3F1.1	Pak Choi and Siew Pak Choi (sawi putch) 白菜和小白菜									A / B / C
3F1.2	Chinese mustard (*Kai Choi*) (sawi asin) 大头菜，芥菜									A / B / C
3F1.3	Chinese chives and flowering Chinese chives (kucai) 韭菜，韭菜花									A / B / C
3F1.4	Kangkong (*Ung choi*) 蕹菜									A / B / C
3F1.5	Choi Sum (sawi hijau) 菜心									A / B / C
3F1.6	Spinach (*Yin choi* and *Po choi*) (bayam) 苋菜, 菠菜, 潺菜									A / B / C
3F1.7	Watercress 西洋菜									A / B / C
3F1.8	Chinese Kale (kailan) 芥兰									A / B / C
3F1.9	Other dark green leaves such as *Kou Kay Choi*, sweet potato leaves (daun keledek) 其它深绿色菜,如枸杞菜, 蕃薯叶									A / B / C
3F1.10	Head cabbage and *Wong Nga Pak* 椰菜 (包菜, 高丽菜), 黄芽白 (大白菜)									A / B / C
3F1.11	Head lettuce and Chinese lettuce 玻璃生菜, 生菜									A / B / C
3F1.12	Broccoli (brokoli) 芥兰花									A / B / C
3F1.13	Cauliflower (bunga kobis) 椰菜花 (高丽菜花)									A / B / C

No 编号	FRESH VEGETABLES 蔬菜品种	a. Frequency and Usual portion size 通常食用的平均次数及份量 CHOOSE ONE according to photograph 请根据相片, 填上您每次所吃的份量: **A** – Small / 小 ; **B** – Medium / 中; **C** – Large / 大								
		Never or less than once a year 一年少于一次或没有	At least once a year but less than once a month 每月少 过一次 但一年 至少一次	1-3 times a month 一个月 1-3 次	Once a week 一个星期一次	2-3 times a week 一个星期 2-3 次	4-6 times a week 一个星期 4-6 次	Once a day 一天一次	2-3 times a day 一天 2-3 次	b. SIZE 份量
3F1.14	Carrots (lobak merah) 胡萝卜 (红萝卜)									A / B / C
3F1.15	Green beans, long beans and peas, snow peas, lentil, soy (kacang hijou / kacang pes) 青豆类, 包括豆角 (菜豆), 荷兰豆 (豌豆), 扁豆类, 大豆类									A / B / C
3F1.16	Bean sprout (taugeh) 豆芽, 大豆芽									A / B / C
3F1.17	Bitter gourd and hairy gourd (peria / timun bulu) 苦瓜, 毛瓜									A / B / C
3F1.18	Potatoes (kentang puteh) 薯仔（马铃薯)									A / B / C
3F1.19	Cucumber (timun) 黄瓜									A - 2 slices/ wedges or less B - 3 or 4 slices/ wedges C - 5 slices/ wedges or more
3F1.20	Tomatoes, cooked or raw (tomato, masak atau mentah) 蕃茄, 煮熟或生吃									A - 2 slices/ wedges or less B - 3 or 4 slices/ wedges C - 5 slices/ wedges or more
3F1.21	Celery (Chinese & English) 芹菜, 西洋芹菜									A / B / C
3F1.22	Ladyfinger 秋葵, 羊角豆									A / B / C
3F1.23	Eggplant / Brinjal 茄子									A / B / C
3F1.24	Seaweed (rumpai laut) 紫菜									A / B / C
3F1.25	Onions, all types (bawang) 葱类, 包括洋葱, 青葱和小葱头									A – < ½ B – ½ onion C – > ½
3F1.26	Corn (jagung muda) 粟米, 玉米, 玉蜀黍									A – ½ ear B – one ear C – > 1 ear
3F1.27	Pumpkin 南瓜									A - 2 slices/ wedges or less B - 3 or 4 slices/ wedges C - 5 slices/ wedges or more
3F1.28	Petai (Stink bean) 臭豆									A / B / C

2.) Fruits (Fresh / Canned) 水果（新鲜或罐头）

We now come to **fresh or canned fruits** that you consumed **during the past year**. For seasonal fruits, please tell me your consumption pattern when the fruits were in season. Includes consumption at home and outside.
现在我们来谈一谈**新鲜或罐头水果**。请您告诉我您在**过去一年**里所吃过的水果。 有些水果是有季节性的，请您告诉我这些水果在上市时您所吃的平均次数和份量（包括您在家和外面吃的）。

No 编号	FRESH FRUITS 水果品种	a. Frequency 平均次数								b. Usual portion size 通常食用的份量 CHOOSE ONE 请任选一项
		Never or less than once a year 一年少于一次或没有	At least once a year but less than once a month 少过一次但一年至少一次	1-3 times a month 一个月 1-3 次	Once a week 一个星期一次	2-3 times a week 一个星期 2-3 次	4-6 times a week 一个星期 4-6 次	Once a day 一天一次	2-3 times a day 一天 2-3 次	
3F2.1	Apple 苹果									A - ½ or less 一半或更少 **B - 1 一个** C - 2 or more 2 个或更多
3F2.2	Orange 橙									A - ½ or less 一半或更少 **B - 1 一个** C - 2 or more 2 个或更多
3F2.3	Tangerine (mandarin orange) 柑 (红柑)									A - ½ or less 一半或更少 **B - 1 一个** C - 2 or more 2 个或更多
3F2.4	Pear 梨									A - ½ or less 一半或更少 **B - 1 一个** C - 2 or more 2 个或更多
3F2.5	Mango 芒果									A - ½ or less 一半或更少 **B - 1 一个** C - 2 or more 2 个或更多
3F2.6	Persimmon 柿子									A - ½ or less 一半或更少 **B - 1 一个** C - 2 or more 2 个或更多
3F2.7	Apricots and peaches 杏, 桃									A - ½ peach or 1 apricot or less 半个桃或一个杏或更少 **B - 1 peach or 2 apricots 1 个桃 或 2 个杏** C - 2 peaches or 4 apricots or more 2 个桃 或 4 个杏或更多
3F2.8	Grapes 葡萄									A - 6 or less 6 粒或更少 **B - 7 to 12 7-12 粒** C - 13 or more 13 粒或更多
3F2.9	Banana 香蕉									A - ½ big or 1 small banana or less ½个大的或一个小的或更少 **B - 1 big or 2 small bananas 一个大的或两个小的** C - 2 big or 3 small bananas or more 2 个大的或 3 个小的或更多
3F2.10	Papaya 木瓜									A - ¼ small or ½ hawker wedge or less /¼小的或 1/2 片或更少 **B - ½ small or 1 hawker wedge ½个小的或 1 片** C - 1 small or 2 hawker wedges or more 1 个小的或 2 片或更多
3F2.11	Honeydew 蜜瓜									A - ½ hawker wedge or less ½片或更少 **B - 1 hawker wedge 1 片** C - 2 hawker wedges or more 2 片或更多
3F2.12	Watermelon 西瓜									A - ½ hawker wedge or less ½片或更少 **B - 1 hawker wedge 1 片** C - 2 hawker wedges or more 2 片或更多
3F2.13	Cantaloupe / Rock melon 甜瓜 (哈蜜瓜)									A - 1/8 fruit or ½ rice bowl cubed pieces or less 1/8 个或 ½片或更少 **B - ¼ fruit or 1 rice bowl cubed pieces ¼个或 1 片** C - ½ fruit or 2 rice bowls cubed pieces or more ½ 个或 2 片或更多
3F2.14	Pineapple 菠萝 (黄梨)									A - 1 hawker wedge or less 1 片或更少 **B - 2 hawker wedge 2 片** C - 3 hawker wedges or more 3 片或更多
3F2.15	Other 其他									
3F2.16	Fruit Juice 果计									_____ 240ml cups 杯

3.) Meat, eggs and dairy products 肉类及蛋类食品

Please tell me how often you ate each of these **meats**, on average, **over the past one year** (including food eaten at home and outside). Please point to the photograph which best shows the amount of meat you ate each time.
请告诉我您在**过去一年里**平均所吃以下不同**肉类食品**的次数（包括您在家和外面吃的）。请您指着相片告诉我你每次所吃的份量。

No 编号	Meats 肉类	a. Frequency and Usual portion size 通常食用的平均次数及份量 CHOOSE ONE according to photograph 请根据相片, 填上您每次所吃的份量: **A** – Small / 小 ; **B** – Medium / 中; **C** – Large / 大								
		Never or less than once a year 一年少于一次或没有	At least once a year but less than once a month 每月少过一次但一年至少一次	1-3 times a month 一个月 1-3 次	Once a week 一个星期一次	2-3 times a week 一个星期 2-3 次	4-6 times a week 一个星期 4-6 次	Once a day 一天一次	2-3 times a day 一天 2-3 次	b. SIZE 份量
3F3.1	**FISH 鱼肉类**									A / B / C
3F3.2	Pan fried fish 煎鱼									A / B / C
3F3.3	Deep fried fish 炸鱼									A / B / C
3F3.4	**CHICKEN 鸡肉类**									A / B / C
3F3.5	Pan fried chicken 煎鸡									A / B / C
3F3.6	Deep fried chicken 炸鸡									A / B / C
3F3.7	**PRAWNS and SQUID 虾和鱿鱼类**									A / B / C
3F3.8	**DUCK 鸭肉类**									A / B / C
3F3.9	**BEEF 牛肉类**									A / B / C
3F3.10	**LAMB / MUTTON 羊肉类**									A / B / C
3F3.11	**PORK 猪肉类**									A / B / C
3F3.12	Pan fried pork 煎猪排									A / B / C
3F3.13	Roasted pork 烧肉									A / B / C
3F3.14	BBQ pork 叉烧									A / B / C
	PRESERVED FOOD 腌制类									
3F3.15	Preserved meat 腌肉 (e.g. Sausage 肉肠, Bacon 烟肉, Ham 火腿, Luncheon meat 午餐肉)									A - <1 B – 1 slice or piece C - >1
3F3.16	Preserved fish 腌鱼 (e.g. Salted fish 咸鱼, smoked fish 薰鱼)									
3F3.17	Preserved vegetable 腌菜 (e.g. pickles 泡菜, salted vegetables 咸菜)									
3F3.18	**EGGS (any form) 蛋类**									A - <1 egg B – 1 egg C - >1 egg

3F3.19	Is your diet over the past year generally similar to your normal adult diet? 你过去一年吃的是不是平常成年的饮食习惯? 1. Yes 是 2. No 不是 (give details 请具体说明_____)

G. BEVERAGES, DAIRY PRODUCT AND SUPPLEMENT 饮料品种, 奶类制品及补充剂

Please select the category that best describes how often you drank each **beverage** and/or **alcohol during the past year**. I would also like to know how much you usually drank each time, including consumption at home and outside the home.
请您告诉我您在**过去一年里**经常饮用的**饮料**和 / 或**酒精类饮料**。 同时请告诉我您每次饮用的份量（包括您在家和外面吃的）。

1) **Non-Alcoholic beverages 非酒精类**

No 编号	BEVERAGES 饮料品种	a. Frequency and Usual portion size 通常食用的平均次数及份量 CHOOSE ONE 请任选一项 **A -** ½ mug or less / ½杯或更少, **B -** 1 mug (250ml) / 1 杯, **C -** 2 mugs or more / 2 杯或更多										b. SIZE 份量
		Never or less than once a year 一年少于一次或没有	At least once a year but less than once a month 每月少 过一次 但一年 至少一次	1-3 times a month 一个月 1-3 次	Once a week 一个星期一次	2-3 times a week 一个星期 2-3 次	4-6 times a week 一个星期 4-6 次	Once a day 一天一次	2-3 times a day 一天 2-3 次	4-5 times a day 一天 4-5 次	6 or more times a day 一天 6 次或更多次	
3G.1	Ceylon tea or western red tea 锡兰茶或西式红茶											A B C
3G.2	Chinese tea 中国茶: - black tea 黑茶(Pu'er 普洱), - Oolong 乌龙茶 (Ti Kuan Yin 铁观音) - white tea 白茶 (Shou Mei 寿眉)											A B C
3G.3	Flower tea 花茶 (Chrysanthemum 菊花茶, Jasmine 茉莉茶 or other flower tea)											A B C
3G.4	Chinese (Lung Ching 龙井) or Japanese Green tea 中国 / 日本绿茶											A B C
3G.5	Coffee (any form) 咖啡											A B C

2) Dairy product 奶类制品

3G.6	Fresh milk e.g with cereal 鲜奶											A B C
3G.7	Condensed or evaporated milk e.g. in coffee or tea 炼奶/淡奶											A B C
3G.8	Yoghurt (including Lassi) 乳酪											A B C
3G.9	Cheese (in any form) 芝士											

3) Supplement use 补充剂

	Type 类型	Duration and Frequency 年期及平均服用量				
3.G10	Multi-vitamins 多种维他命	a. Duration of regular use	1. 0-1 years	2. 2-4 years	3. 5-9 years	4. ≥ 10 years
		b. No. taken per week	1. ≤2	2. 3-6	3. 7 or more	
3.G11	Vitamin C 维他命 C	a. Duration of regular use	1. 0-1 years	2. 2-4 years	3. 5-9 years	4. ≥ 10 years
		b. No. taken per week	1. ≤2	2. 3-6	3. 7 or more	
3G.12	Folate / Folic Acid 葉酸	a. Duration of regular use	1. 0-1 years	2. 2-4 years	3. 5-9 years	4. ≥ 10 years
		b. No. taken per week	1. ≤2	2. 3-6	3. 7 or more	
3G.13	Calcium 鈣	a. Duration of regular use	1. 0-1 years	2. 2-4 years	3. 5-9 years	4. ≥ 10 years
		b. No. taken per week	1. ≤2	2. 3-6	3. 7 or more	
3G.14	Others (please state) 其他 (请具体说明_____	a. Duration of regular use	1. 0-1 years	2. 2-4 years	3. 5-9 years	4. ≥ 10 years
		b. No. taken per week	1. ≤2	2. 3-6	3. 7 or more	

4) Alcohol intake 酒精类

3G.15	Have you ever drunk alcohol (such as beer, rice wine, red/white wine or spirit/hard liquor) more than once a month, on average? 您從来有没有喝过酒（如：啤酒，米酒，紅/白酒烈性酒）平均超过每月一次？ (if no, go to Question 3.H1 如果没有，直接转到问题 3.H1)	1. Yes 有 2. No 没有
3G.16	How old were you when you start drinking one or more times per month? 您从什么时候开始喝超过每月一次？	_____ Years old 岁

		a. How often did you drink these specific types of alcohol？ 您多久喝一次以下的酒类?	b. On the day you drink, how many drinks, on average, did you have？ 喝酒那天，平均喝多少？
3G16.1	Beer, lager, stout, shandy, or cider 啤酒类	1. Never or <1/mth 从来没有 到 少于每月一次 2. 1/mth to <1/week 每月一次 到 少于每星期一次 3. _____days/week 每星期_____天	_____ glasses/day 杯/天 _____ cans/day 罐/天 _____ small bottles/day 小瓶/天 _____ large bottles/day 大瓶/天
3G16.2	Rice wine, Japanese Sake 米酒, 日本清酒	1. Never or <1/mth 从来没有 到 少于每月一次 2. 1/mth to <1/week 每月一次 到 少于每星期一次 3. _____days/week 每星期_____天	_____ glasses/day 杯/天 _____ cans/day 罐/天 _____ small bottles/day 小瓶/天 _____ large bottles/day 大瓶/天
3G16.3	Red / white wine / sherry 葡萄酒类 (紅/白酒)	1. Never or <1/mth 从来没有 到 少于每月一次 2. 1/mth to <1/week 每月一次 到 少于每星期一次 3. _____days/week 每星期_____天	_____ glasses/day 杯/天 _____ small bottles/day 小瓶/天 _____ large bottles/day 大瓶/天
3G16.4	Spirit / Hard liquor (e.g. brandy) 烈性酒 (如白兰地)	1. Never or <1/mth 从来没有 到 少于每月一次 2. 1/mth to <1/week 每月一次 到 少于每星期一次 3. _____days/week 每星期_____天	_____ glasses/day 杯/天 _____ small bottles/day 小瓶/天 _____ large bottles/day 大瓶/天

1 drink = 330 ml of beer / 150mls of wine / 30ml of spirit = 12 – 15g of ethanol

H. SMOKING 吸烟习惯

1). Personal smoking 个人吸烟

3H.1	Have you ever smoked a cigarette in your lifetime? 您從来有没有曾经抽过香烟?	1. Yes 有 2. No 没有
3H.2	Have you ever smoked or chewed any form of tobacco apart from manufactured cigarettes ? 您從来有没有曾经抽过/咬过任何烟草类产品 (除了香烟)? (if no to ***both*** H1 and H2, go to Question 3H.11)	1. Yes 有 2. No 没有
3H.3	If yes, please specify 如果有，请具体说明	Type 类 _____No. of years used _____ _____年
3H.4	Have you smoked at least 100 cigarettes (or any other form of tobacco) in your lifetime? 到目前为止您抽超过 100 根烟 (或其它烟草类产品) 吗?	1. Yes 有 2. No 没有
3H.5	Have you ever smoked at least one cigarette (or any other form of tobacco) a day for 1 year or more? 您是否一天至少抽一根烟 (或其它烟草类产品) 长达一年或更长时间? (if no, go to Question 3H.11 如果没有，直接转到问题 3H.11)	1. Yes 有 2. No 没有
3H.6	At what age did you start smoking? 您从几岁开始抽烟?	_____ Years 年
3H.7	On average, how many days per week do / did you usually smoke? 您平均一个星期抽几天烟? 1. Daily 每天 2. 4-6 days a week 一个星期 4-6 天 3. 2-3 days a week 一个星期 2-3 天 4. Once a week 一个星期一次 5. Less than once a week 一个星期少过一次	
3H.8	How many sticks do you smoke in a day (1 pack = 20 sticks)? 您大概一天抽多少根香烟 (一包=20 根) ?	_ Sticks 根
3H.9	Have you smoked at least one cigarette in the past 30 days? 您是否在过去 30 天内抽过至少一根香烟?	1. Yes 有 2. No 没有
3H.10	(If 3H.9 is "No") At what age did you stop smoking? (如果 3H.9 没有) 您在多大年纪停止抽烟?	_ Years 年

2). Passive smoking 二手烟

Home 家庭	
3H.11	Has any of your household members smoked cigarettes **at home** at least daily for 1 year or longer? 您家里是否有成员每天**在家里抽烟**长达一年以上? 1. Yes 是 2. No / not daily 否 / 不是每天 (go to Question 3.H14)
3H.12	Who smokes or smoked daily at home? 谁每天在家里吸烟? 1. Spouse 配偶 2. Others e.g. parents / in-laws / son / daughter / relatives 其他人, 如父母 / 亲家 / 儿女 / 亲戚 3. Both 以上都是
3H.13	For how many years has at least one person living in your home smoked daily at home? 在您家里至少有一个人每天吸烟长达多久时间? 1. less than 5 years 少于 5 年 2. 5– 9 years 5-9 年 3. 9– 14 years 10-14 年 4. 15 – 19 years 15-19 年 5. 20 or more years 20 年或更长时间

Work place 工作环境		
3H.14	Have you ever had a job where you were in close contact with, or close enough to smell cigarette smoke on a daily basis? 您有没有每天在附近有人吸烟，或者可以闻到香烟气味的环境中工作过?	1. Yes 有 2. No 没有 (Go to Q3I.1) 3. NA (never employed outside home)
3H.15	For how many years were you in contact with cigarette smoke at work? 请问 这种情况持续多少年?	_____ Years 年
3H.16	For how many hours a day did this occur? 请问这种情况每天持续多少时间?	_____ Hours 小时

I. Tattoo / Acupuncture 纹身及针灸

3I.1	Have you ever had a **permanent tattoo**? (including eyebrow) 您有没有纹身 （包括纹眉）?	1. Yes 有	2. No 没有
3I.2	If yes, how old were you when you first started having a tattoo? 如果有，从几岁开始?	**Age** **年龄**	_____ yrs old 岁
3I.3	How many times have you been tattooed in your lifetime? 您一共做过多少次?	**No. of times** **次数**	_____ times 次

3I.4	Have you ever had **acupuncture** performed on you? 您有没有做过针灸治疗?	1. Yes 有	2. No 没有
3I.5	If yes, how old were you when you first had acupuncture? 如果有，从几岁开始?	**Age** **年龄**	_____ yrs old 岁
3I.6	How many times have you had acupuncture in your lifetime? 您一共做过多少次?	**No. of times** **次数**	_____ times 次

PART IV. Family History 家庭资料

A. Family Medical History 家庭病历

4A.1 Has any of your family members (parent, sister / brother or child) ever had cancer? Note: only full siblings are included. 您的家庭成员（父母，兄弟姐妹或孩子）中有谁得过癌症吗？注意：只包括亲生的兄弟姐妹

[1.] no (skip to 4A.3) 没有(跳到 4A.3)

[2.] yes, one family member has ever had cancer 有，有一位家庭成员患有癌症

[3.] yes, two or more family members have ever had cancer 有，有两位或以上家庭成员患有癌症

4.A1a	Father 父亲	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A1b	Mother 母亲	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A1c	Brother 兄弟	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A1d	Sister 姐妹	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A1e	Son 儿子	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A1f	Daughter 女儿	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道

[4.] Unknown 不知道

4A.2 If yes, What type of cancer did he / she have? (if more than one, record all sites) Please specify. (Fill in the table below for each relative affected) 如果有，他(或她)患有何种癌症？请具体说明。

	a. Relatives affected 亲戚	**Cancer site 癌症位置**		**d. Age at diagnosis 初诊年龄**
		b. Site 位置	**c. ICD Code**	

4.A3 Has any of your family members (parent, sister / brother or child) ever had disease of the liver, such as cirrhosis or hepatitis ? 您的家庭成员（父母, 兄弟姐妹或孩子）中有谁得过肝病，例如肝硬化或肝炎?

[1.] no (skip to next section) 没有(跳过此项到下一部分)

[2.] yes, one family member has ever had 有，有一位家庭成员患有

[3.] yes, two or more family members have ever had 有，有两位或以上家庭成员患有

4.A3a	Father 父亲	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A3b	Mother 母亲	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A3c	Brother 兄弟	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A3d	Sister 姐妹	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A3e	Son 儿子	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道
4.A3f	Daughter 女儿	[1.] Yes 是 / [2.] No 否 / [3.] Don't know 不知道

[4.] Unknown 不知道

B. RESIDENTIAL HISTORY 居住简历

Please try to remember the residences in which you have lived for **more than a year**. We will start from the first house you lived in after you were born. For each house, I will ask you about different aspects.

请想起您从前**曾经居住超过一年**的房子， 我们会从您出生开始计算。 这些问题包括不同的类型。

		a. HOUSE 1 房子一	b. HOUSE 2 房子二	c. HOUSE 3 房子三	d. HOUSE 4 房子四	e. HOUSE 5 房子五	f. HOUSE 6 房子六
4B.1	Age start 最初年龄	**00**					
4B.2	Age end 最后年龄						
4B.3	With whom did you share the house? 跟谁住在一起? 1.Family 家人 2.Boarding School 寄宿学校 3.Institution 学院/团体 4.Friends 朋友 5.Others 其他						
4B.4	Nº of bed rooms 睡房 – 房间总数						
4B.5	What is the maximum number of people in the household? 最多可以有多少人一起住?						
4B.6	How many family members shared the same bed-room with you? (inclusive) 您和多少家人共睡一房间?						
4B.7	Country 国家 District / area 地区						
4B.8	Rural / Urban 乡村的 / 都市的	R / U	R / U	R / U	R / U	R / U	R / U
4B.9	Water source 水源 Pipe 水管 or Well/pump 井水/ 抽水	Pp / W	Pp / W	Pp / W	Pp / W	Pp / W	Pp / W

Did you have contact with any of the following animals? 您有沒有接触以下列出的动物?

		a. HOUSE 1 房子一	**b. HOUSE 2 房子二**	**c. HOUSE 3 房子三**	**d. HOUSE 4 房子四**	**e. HOUSE 5 房子五**	**f. HOUSE 6 房子六**
4B.10	**Type 1: small animals (e.g. dogs, cats)** **第一类 ： 小型动物, 狗或猫科等**	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有
4B.11	Animal lives 动物住在 : 1. indoors 室内的 2. outdoors 屋外的						
4B.12	Contact 接触 1. None 从来没有 2. Occasional 有时 3. Frequent 时常 4. Daily 每日						
4B.13	**Type 2 : Birds, hens** **第二类 ： 鸟类, 鸡类**	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有
4B.14	Animal lives 动物住在 : 1. indoors 室内的 2. outdoors 屋外的						
4B.15	Contact 接触 1. None 从来没有 2. Occasional 有时 3. Frequent 时常 4. Daily 每日						
4B.16	**Type 3 : Big animals (e.g. horses pigs, cows).** **第三类 ： 大型动物, 马, 猪, 牛**	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有	Y / N 有 / 沒有
4B.17	Contact 接触 1. None 从来没有 2. Occasional 有时 3. Frequent 时常 4. Daily 每日						

PART V. QUALITY

1. Interviewer's assessment of the reliability of the answers:

Mark rank

1	2	3	4	5

Not very reliable Very reliable

2. Has the interviewed person felt uncomfortable

☐ Yes In which questions _____

☐ No

3. Length of interview (mins) : _____

4. Write down any comments you may have on the interview

_____

_____

_____

_____

_____

_____

Checked

_____ _____

Interviewer's signature *Coordinator's signature*

Primary site _____ *ICDO-3* | *C* | | | |

*Nodal / Extranodal** *ICDO-3* *C*

Histological diagnosis (WHO) _____ | *M* | | | | | |

_____

*Grade : High / Intermediate / Low** *Stage :* _____

Data entry by : _____ *(Name) on* _____ *(date)*

Data entry checked by : _____ *(Name) on* _____ *(date)*

*Delete as appropriate

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Occupation and risk of non-Hodgkin's lymphoma in Singapore

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Background Some epidemiological studies have reported that teachers may be at increased risk of non-Hodgkin's lymphoma (NHL), but results are inconsistent.

Aims To examine the possible association between occupation and risk of NHL in the Singapore population.

Methods A hospital-based interviewer-administered case–control study was carried out in five major hospitals in Singapore between April 2004 and December 2008. A complete occupational history, which included all jobs lasting over 1 year since graduation from school, was obtained for each participant. The Singapore Standard Occupational Classification was used for coding all occupations recorded.

Results Eight hundred and thirty controls and 465 NHL cases, comprising B-cell (n = 404, 87%) as well as T- and NK-cell (n = 61, 13%) neoplasms, were recruited. Having ever worked as a teacher was associated with a significantly higher risk of NHL (adjusted OR 2.04, 95% CI 1.12–3.72). Teachers who had taught for ≤10 years had a significantly higher risk of NHL (adjusted OR 2.44, 95% CI 1.11–5.34), but we did not observe an elevated risk for those who reported teaching for >10 years. Among the 31 teachers with NHL, 23% taught in upper secondary schools, with equal proportions (13%) teaching in primary and pre-primary schools, respectively. The remainder taught in other settings.

Conclusions Teachers come into frequent contact with children and may consequently have higher rates of exposure to common infectious agents. Therefore, the hypothesis of an infective aetiology of NHL may be supported by our findings.

Key words Non-Hodgkin's lymphoma; occupation; risk factor; teacher.

Introduction

Non-Hodgkin's lymphoma (NHL) is one of the 10 most frequently occurring cancers in both men and women in Singapore, and its incidence has more than doubled in the last three decades. The age-adjusted incidence rates for males and females (per 1 00 000) for NHL in Singapore have increased from 3.1 and 1.9 in 1968–72 to 8.2 and 5.0 in 1998–2002, respectively [1].

Although the risk factors for NHL include inherited and acquired immunodeficiency conditions [2], infectious, physical and chemical agents have also been implicated [3]. At present, no conclusive evidence of causal relations between occupation and increased NHL risk exists. In a recent review of occupation and risk of NHL, Boffetta and de Vocht [4] reported significantly increased risk among workers in the printing industry, wood workers, farmers (especially in animal husbandry) and teachers. Possible aetiological agents suggested were organic solvents, insecticides and viral infection. The increasing incidence of NHL in Singapore might be influenced by changes in working patterns resulting from its development from a trading port in the 1950s and 1960s to a rapidly industrialized society in the 1970s and beyond. This study aimed to examine possible associations between occupation and risk for NHL in Singapore.

Methods

The Singapore Lymphoma Study is a hospital-based case–control study carried out in five major hospitals in Singapore, between April 2004 and December 2008. The study population was Singapore citizens or permanent residents aged ≥18 years. The study was approved by research ethics committees at each participating hospital.

Details of the methodology have been described elsewhere (Wong *et al.*, submitted for publication). Eligible subjects were patients with NHL diagnosed within the past 6 months and histologically confirmed according to the World Health's Organization's classification system [5]. Hospital controls were frequency matched with cases by recruitment centre, age (±5 years) and gender, with an approximate ratio of two controls to one case. Controls were patients admitted primarily for acute diagnoses to orthopaedic, internal medicine and general surgery wards. Patients with a prior history of HIV infection were not recruited.

Data were collected in person via a standardized questionnaire-based interview. The questionnaire was based on the instrument used by the Epilymph consortium modified for local use in Singapore [6].

We elicited a complete occupational history that included all jobs lasting over 1 year since graduation from school. For every job information collected included the year in which employment began and ended the job title and the industry and a description of work activities including any use of chemicals or operation of machinery. The Singapore Standard Occupational Classification (SSOC) was used for coding occupation for all subjects [7]. The SSOC adopts the basic framework and principles of the International Standard Classification of Occupations 1988 (ISCO-88). It is reviewed and updated periodically to reflect changes in the employment structure and the emergence of new occupations in Singapore.

The SSOC comprises five-digit codes with each digit giving increasing specificity regarding the individual occupation. The one-digit code represents a very broad field of work (e.g. 'Professional' is coded as '2'), whereas the two-digit codes provide a more specific description (e.g. code '23' denotes 'teaching professionals').

For this study, we used the first and longest occupations to examine the association between occupation and NHL. The first occupation was the first job that the subject took up after leaving school or their first job if they had not attended school. The longest occupation was determined on the basis of the duration of each occupation reported; if the subject took up the same job on more than one occasion, the total duration in years was used for this purpose.

An unconditional logistic regression model was used to calculate odds ratio (OR) and 95% confidence intervals (CIs) for the association between occupation and the risk of lymphoma. All analyses were adjusted for age (as a continuous variable), gender, ethnic group (Chinese, Malay, Indian, others), history of cancer in first-degree relatives (yes, no) and current housing type (public housing three or less rooms, public housing more than three rooms, private housing, others). Analyses were performed with STATA/SE 10.1 software (StataCorp, TX, USA, 1984–2009). All statistical tests were two sided.

Results

Eight hundred and thirty controls and 465 NHL cases were recruited, comprising B-cell (n = 404, 87%) as well as T- and NK-cell (n = 61, 13%) neoplasms. Compared with controls, cases were more likely to be Chinese, married, currently employed, born outside Singapore and residing in larger apartments or landed property. Among 830 controls and 465 NHL cases, 760 controls and 429 NHL cases were currently employed or had retired and 69 controls and 31 NHL cases had never been employed (e.g. students, housewives, etc.). A total of 12 controls and 6 NHL cases did not disclose a detailed occupational history and were treated as missing data. The current analysis focused on 749 controls and 428 NHL cases who provided detailed occupational histories.

In both the first and longest occupations, using the one-digit code of the SSOC, there was a significantly higher percentage (9 and 8%, respectively) of professionals with NHL compared to the controls (4 and 5%, respectively) (Table 1). The distribution of professionals for first and longest occupation among the cases and controls was further examined using two-digit SSOC codes. A significantly higher proportion of cases than controls reported being a teaching professional as their longest occupation. Teaching and 'business professionals' also constituted a higher proportion of first occupations among cases than controls. The number of business professionals was too small (one control and nine cases) for further analysis.

We proceeded to examine the association between teachers and NHL. Table 2 shows the OR for those who had ever been teachers versus other occupations. Teachers as compared to non-teachers had a significantly higher risk of NHL (adjusted OR 2.04, 95% CI 1.12–3.72). Teachers who had taught for 1–10 years had significantly higher risk of NHL (adjusted OR 2.44, 95% CI 1.11–5.34), but we did not observe an elevated risk for those who reported teaching for >10 years. Among the 31 teachers with NHL, 23% taught in upper secondary schools, with equal proportions (13%) teaching in primary and pre-primary schools. The others were private tutors (13%) or professionals engaged in other forms of teaching (39%) not otherwise classified.

Discussion

We have found that teachers appear to have a 2-fold elevated risk of NHL compared with non-teachers in Singapore. The strength of this study, involving 465 incident cases of NHL and 830 controls, is that it is the largest case–control study of NHL ever conducted in an Asian country. There are, however, limitations in our study. While we could adjust for some possible confounders, there will be other factors that we may not have

Table 1. Distribution of the first and longest occupations among the NHL cases and controls in the Singapore Lymphoma Study

SSOC	Controls[a] *n* (%)	NHL[a] *n* (%)	Total *n* (%)	*P*-value[b]
First occupation				
1 Legislators, senior officials and managers	27 (4)	20 (5)	47 (4)	NS
2 Professionals	33 (4)	40 (9)	73 (6)	**
3 Associate professionals and technicians	61 (8)	39 (9)	100 (8)	NS
4 Clerical workers	86 (12)	57 (13)	143 (12)	NS
5 Service workers and shop and market sales	132 (18)	64 (15)	196 (17)	NS
6 Agricultural and fisher workers	21 (3)	17 (4)	38 (3)	NS
7 Production craftsmen and related workers	96 (13)	53 (12)	149 (13)	NS
8 Plant and machine operators and assemblers	142 (19)	62 (14)	204 (17)	NS
9 Cleaners, labourers and related workers	137 (18)	69 (16)	206 (18)	NS
10 Workers not classifiable by occupation	14 (2)	7 (2)	21 (2)	NS
Total number of first occupations[a]	749 (100)	428 (100)	1177 (100)	
Longest occupation				
1 Legislators, senior officials and managers	45 (6)	33 (8)	78 (7)	NS
2 Professionals	38 (5)	35 (8)	73 (6)	*
3 Associate professionals and technicians	85 (11)	52 (12)	137 (12)	NS
4 Clerical workers	90 (12)	52 (12)	142 (12)	NS
5 Service workers and shop and market sales	139 (19)	62 (14)	201 (17)	NS
6 Agricultural and fisher workers	10 (1)	7 (2)	17 (1)	NS
7 Production craftsmen and related workers	80 (11)	50 (12)	130 (11)	NS
8 Plant and machine operators and assemblers	129 (17)	77 (18)	206 (18)	NS
9 Cleaners, labourers and related workers	119 (16)	55 (13)	174 (15)	NS
10 Workers not classifiable by occupation	12 (2)	5 (1)	17 (1)	NS
Total number of longest occupations[a]	747 (100)	428 (100)	1175 (100)	

NS, not significant.

[a]Total numbers did not add up to 830 controls and 465 NHL cases due to missing information.

[b]*P*-value from chi-square test of significance between group of interest versus others: NS, $*P < 0.05$, $**P < 0.01$.

Table 2. ORs and 95% CIs for the association between teaching and risk of NHL

	Controls ($n = 749$) *n* (%)	NHL ($n = 428$) *n* (%)	Crude OR (95% CI)[a]	*P*	Adjusted OR (95% CI)[b]	*P*
Non-teachers	724 (97)	397 (93)	1.00 (referent)		1.00 (referent)	
Ever teachers	25 (3)	31 (7)	2.26 (1.32–3.88)	**	2.04 (1.12–3.72)	*
Duration						
1–10 years	15 (2)	17 (4)	2.07 (1.02–4.18)	*	2.44 (1.11–5.34)	*
>10 years	10 (1)	14 (3)	2.55 (1.12–5.80)	*	1.61 (0.66–3.93)	NS

n, number of subjects; *P*-value: NS, $*P < 0.05$, $**P < 0.01$.

[a]Crude OR in logistic regression.

[b]Adjusted OR for age (continuous), gender (male/female), ethnicity (Chinese/Malay/Indian/others), housing type (public housing three or less rooms/public housing more than three rooms/private housing/others) and family history of cancer in the first-degree relatives (yes/no) in multiple logistic regression model.

considered or have information on. Compared to a national registry, the number of NHL cases in this study was much smaller. We are currently unable to determine the likely causative agent. In a prospective cohort study, if biological samples were collected, it would be more feasible to carry out serological analyses, e.g. the distribution of Epstein–Barr virus titres among those who developed NHL and those who did not.

Since 1983, there have been reports of an increased standardized cumulative incidence ratio (SIR) for NHL among teachers [8]. In a large registry-based analysis in Sweden, researchers used the Swedish Cancer-Environmental Registry to link cancer incidence during 1961–79 with occupational information from the 1960 census; this study reported an SIR among schoolteachers of 2.1 ($P < 0.05$). When they included specific occupations within this industry, they found that 'schoolteachers in other education' had an SIR of 3.8 ($P < 0.05$) [9]. The paper does not mention what 'other education' involved. This study, being registry based, had no additional

information on exposures and duration of employment in order to explore further possible causes for the association. The authors commented that 'whether carcinogenic exposures occur among these workers is not clear, although socioeconomic and dietary factors may also be important' [9]. Boffetta and de Vocht [4] conducted a meta-analysis to provide an update on occupation and the risk of NHL. They reported among other occupations an increased risk for teaching (relative risk 1.47, 95% CI 1.34–1.61). This observation was based on 19 reported studies published up to August 2006.

Infectious agents are close to being regarded as established aetiological agents for NHL [10]. Teachers and childcare workers have been reported to be more at risk of contracting infectious diseases [11,12]. Teachers inevitably come into close contact with children frequently in the course of their work. In Singapore, teacher to student ratios could be as high as 1:40, especially in the 1960s and 1970s. However, we found no evidence of a dose–response relationship, as those who taught for 1–10 years had a significantly higher risk of NHL (adjusted OR 2.44; 95% CI 1.11–5.34) compared to non-teachers, whereas the OR for those who had taught for >10 years was not significant when compared with non-teachers. This observation might be consistent with the involvement of an infectious agent, which may not require prolonged exposure (unlike for example chemical exposure) to exert its effects on the individual's health. Whether we took the first occupation or the longest occupation, teachers still appeared to be at increased risk of NHL. Our findings are in agreement with other studies, which also reported no statistically significant differences between teachers in primary and secondary education [4,13].

Among the 31 'ever-teachers' cases, 48% were teaching in the secondary, primary and pre-primary schools, which covers children between 3 and 16 years old. However, 13% were private tutors and 39% professionals engaged in other forms of teaching not otherwise classified. We were not able to ascertain whether this 52% were exposed to children in their adolescence and early childhood. If this 52% of teachers with NHL were not exposed to children, it would weaken the hypothesis of an association with infectious agents.

While most studies [3,4,9] have found a strong association between NHL and farmers, we did not. This is not surprising as Singapore is not an agricultural country and has never been because of its small land area (710 km^2). Likewise, we did not find any association between NHL and industrial workers (such as printers and cleaners), which have also been reported by other studies [4,14,15]. This is more difficult to explain, unless such workers in Singapore have not been exposed to significant levels of whatever specific chemicals may be capable of contributing to the development of NHL.

Key points

- There have been previous reports of associations between non-Hodgkin's lymphoma and certain occupations, including teachers, mostly in western populations.
- We found that among an Asian population, teachers have higher odds for developing non-Hodgkin's lymphoma than other occupational groups.
- This finding could lend support to the hypothesis of an infective aetiology of non-Hodgkin's lymphoma.

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Conflicts of interest

None declared.

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ORIGINAL PAPER

Sun exposure and risk of lymphoid neoplasms in Singapore

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Abstract
Background Epidemiologic studies have reported an inverse association between sun exposure and non-Hodgkin lymphoma (NHL), but these have been almost exclusively conducted in Western populations residing in temperate locations. We evaluated the association between personal outdoor sun exposure and risk of malignant lymphomas in Singapore.
Methods A hospital-based case–control study of 541 incident cases of lymphoid neoplasms and 830 controls were recruited during 2004–2008. Participants were interviewed regarding recreational or occupational outdoor activities during childhood and in adulthood. Basic demographics and potential confounders were also collected. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated using unconditional logistic regression analysis.
Results Compared with individuals who did not have regular sun exposure, a lower risk of NHL was observed for those who reported regular exposure on non-school days during childhood [OR, 0.62; 95 % CI, 0.46–0.83] and non-working days in adulthood [OR, 0.70; 95 % CI, 0.51–0.97]. The protective effect was more evident among women.
Conclusion Our findings support an inverse relationship between intermittent sun exposure and the risk of NHL. These findings are consistent with the growing evidence from various countries, but further studies, especially prospective studies, are needed in Asian populations.

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Keywords Case–control study · Non-Hodgkin lymphoma · Occupational sun exposure · Recreational sun exposure · Risk factors

Introduction

Lymphoid neoplasm (LN), a heterogeneous group of cancers arising in the lymphoid tissue, is one of the least understood and most complex group of cancers. The World Health Organization (WHO) classification groups them into B-cell neoplasms, T-cell neoplasms and Hodgkin lymphoma (HL) [1]. The B- and T-cell types are commonly known as non-Hodgkin lymphoma (NHL).

LN is among the ten most frequent cancers in Singapore and accounted for 6 and 4.2 % of all cancers in Singapore men and women, respectively, in 2003–2007 [2]. In the past few decades, the incidence and mortality rates for NHL have been increasing substantially worldwide [3]. However, the increase appears to have begun to level off in Europe in recent years [4]. In Singapore where incidence rates of NHL were the highest in south-east and east Asia, the age-standardized incidence rates in men and women have both been rising consistently from 3.1 and 1.9 (per 100,000 person-years) in 1968–1972 to 10.0 and 6.7 (per 100,000 person-years) in 2003–2007, respectively [5]. Only a proportion of lymphomas are known to be related to inherited or acquired immunosuppression (e.g., AIDS or organ transplant procedures) [6, 7], autoimmunity, viral infection or occupational exposures; and they are thought to increase risk only in specific subtypes [8], but much of the etiology remains unexplained.

Cartwright et al. reported in 1994 that in various populations, parallel increases in the incidence of both NHL and non-melanoma skin tumors were noted, based on an analysis using registry data [9]. Large population-based studies also observed an increased risk of subsequent NHL among patients with skin cancer, or vice versa [10, 11]. These findings led to the suggestion that ultraviolet (UV) irradiation may be a common risk factor for both these cancers, possibly through its effects on the immune system. The theory appeared to be supported by several ecologic studies that found positive associations between ambient UV radiation at various geographical latitudes and incidence and mortality from NHL [12–14]. But other similar studies did not support this association [15, 16] or reported inverse associations instead [17–19]. Similarly, both protective [20] and risk conferring [21] effects were observed in the prospective cohort studies examined the association of NHL and UV radiation using area of residence.

More recently, case–control studies that evaluated individual sun exposure levels have generally [22–24], though not uniformly [25], supported a protective effect of leisure-time sun exposure on NHL. In contrast, the effect of occupational sun exposure is much less consistent [26–28]. A pooled analysis conducted by the International Lymphoma Epidemiology Consortium (InterLymph) [23] found a 23 % reduction in risk for men and women in the highest quartile of recreational sun exposure, but no association with non-recreational sun exposure.

To date, all the epidemiologic studies have been conducted in Caucasian populations residing in the United States, Europe, and Australia. Singapore is a multi-ethnic Asian population comprising 4.8 million people, of which 77 % are Chinese, 14 % Malays, and 8 % Indians. The country lies at the southern tip of the Malayan peninsula, at a latitude of one degree north of the equator. The aim of our study was to evaluate the association between personal sun exposure and lymphoma risk in an Asian population residing in a tropical location with consistently high sun exposure throughout the year.

Methods

Study population

The Singapore Lymphoma Study is a hospital-based case–control study carried out in 3 major public hospitals (National University Hospital, Singapore General Hospital, and Tan Tock Seng Hospital) and 2 national referral centers for skin disease (National Skin Centre) and cancer (National Cancer Centre).

Eligible cases were all Singapore residents aged 18 years and above with newly diagnosed lymphoid neoplasm (ICD-O M9590-9596, M9650-9667, M9670-9699, M9700-9729, M9731-9734, M9823-9831, and M9940-9948) including mature B- and T-cell neoplasms and Hodgkin lymphoma. Histological diagnosis and classification were made according to the 2001 WHO classification system [1]. Controls were patients admitted to orthopedic, internal medicine, and general surgery departments in the same hospitals, and whose current admission was not for any of the following: diagnosis or suspicion of malignancy, asthma, atopic eczema or allergy, immune-related disorders, peptic ulcer disease, viral hepatitis, or tuberculosis. Controls were frequency-matched for age (±5 years), gender, study center, and month of diagnosis. Any lymphoma patients or hospital controls with a history of HIV/AIDS or organ transplant were excluded. The study was approved by the Institutional Review Board or Ethics Committee at each participating hospital or institution. Written informed consent was obtained from all participants.

Data collection

The questionnaire used in the Singapore Lymphoma Study was developed with reference, in part, to the questionnaire

originally developed and used by the EpiLymph Group, and modified for local use. A pilot study was conducted between April and October 2004, while the main study was carried out between February 2005 and December 2008. A face-to-face interview in hospital was carried out by trained research staff. Interviews were conducted in the language (English, Malay, or Chinese dialect) which the participant was most familiar with and were taped for quality control purposes with the consent of the interviewee.

In relation to sun sensitivity, participants were asked about skin color (white or light tan, tan, dark brown, or black on the inner side of the arm), eye color (black or dark brown, light brown, other) and natural hair color (black, dark brown, light brown, other). Other variables included history of sunburn (frequency and age at first sunburn), the use of sun protection (including hat, sun-cream, long sleeves or umbrella), and the skin reaction to strong sunlight without any protection (severe sunburn with blistering, painful sunburn followed by peeling, mildly burnt and some tanning, go brown without sunburn).

The number of hours spent on leisure activities under the sun or working outdoors was used as a surrogate for sun exposure. We asked for complete occupational histories of jobs that lasted over 1 year. Information included the year they started and ended each job, occupational title and industry, and the average daily hours of exposure to the sun for every job.

Participants were asked how many hours they spent outdoors regularly on activities such as swimming, sailing, jogging, playing tennis, etc. on school days or weekends in childhood (i.e., <20 years of age), and on working days or rest days in adulthood (i.e., 20 years of age and above). "Outdoor" was defined as not under any shade and between 9 am and 5 pm.

Detailed information on personal demographics, family history of cancer, and other potential confounders were also collected. These included usual adult body weight and height; general physical activity in the past one year in terms of hours spent on activities of (1) vigorous intensity (i.e., strenuous sports of tennis/swimming laps, loading or unloading trucks, shoveling or equivalent manual work), (2) moderate intensity (i.e., heavy housework, light sports including brisk walking/tai chi/bowling), (3) light intensity (including sitting), and (4) sleeping on weekdays and weekends were also recorded.

Statistical analysis

Recreational sun exposure

Measures of recreational sun exposure were constructed for the statistical analysis as follows: Daily exposure was defined as "regular" if at least 30 min per day was spent on outdoor recreational activities on a regular basis; separately for (1) school days and (2) non-school days in childhood, (3) working days, and (4) non-working days in adulthood. The daily exposure was capped at 8 h per day. Weekly exposure was calculated by adding up the daily exposure reported over 5 school days and 2 non-school days in childhood (i.e., childhood per week), and 5 working days and 2 non-working days in adulthood (i.e., adult per week). The weekly exposure was capped at 56 h per week. The unexposed group served as the reference category.

Occupational sun exposure

For occupational sun exposure assessment, participants were defined as outdoor workers if they had spent at least 30 min working outside under sun (between 9 am and 5 pm) in any of the jobs that lasted 1 year or more. We categorized participants into "indoor work only" workers, and those who spent all or part of their working hours outdoors "mixed indoor ± outdoor" workers.

Other variables

Usual adult body height and weight were expressed as body mass index (BMI, kg/m^2). Physical activity of different intensities was converted to metabolic equivalent levels (MET), defined as the ratio of work metabolic rate to standard resting metabolic rate [29], in order to compute the total energy expenditure per week.

An unconditional logistic regression model was used to quantify the effect of outdoor sun exposure on the risk of malignant lymphoma via the odds ratio (OR) estimate and its 95 % confidence interval (CI). All analyses were adjusted for age (as a continuous variable), gender (male/female), ethnic group (Chinese/Malay/Indian), skin color (white or light tan/tan/dark brown or black), education level (no formal education/≤6 years/7–10 years/>10 years), current housing type (public housing ≤3 rooms/public housing >3 rooms/private housing/others) as a surrogate for socio-economic status, BMI (continuous), and history of any cancer in a first-degree relative (yes/no). We further assessed the interaction effect of sun exposure by gender in the multivariable model. Individuals with missing data for any variables were excluded for that analysis. All statistical tests were evaluated assuming a two-sided test at the 0.05 level of significance. Analyses were performed with STATA/SE 10.1 software. (StataCorp, Texas 77845 USA, 1984–2009).

Results

Of the 603 eligible cases ascertained during recruitment period, 62 (10.3 %) did not agree to participate in the study, leaving 541 cases (315 men and 226 women)

(response rate 89.7 %). Among 1,330 controls ascertained and initially confirmed as eligible, 500 (37.6 %) refused to participate and 830 controls were used in this analysis (response rate 62.4 %).

Descriptive characteristics of the study population are summarized in Table 1. The average age of cases and controls was 54.2 years (SD, 16.0) and 50.3 years (SD, 16.0), respectively, with 60 % male participants. Malays and Indians were overrepresented among controls compared with cases. As compared with controls, more cases lived in private housing (12.9 vs. 4.9 %) and had positive family history of any cancer in the first-degree relatives (34.4 vs. 21.7 %). More cases were born outside Singapore/Malaysia (10.1 vs. 5.3 %), only 14 cases (2.6 %) and 9 controls (1.1 %) immigrated to Singapore after age 20. The mean usual adult BMI in the controls (25.0 kg/m^2; SD, 5.3) was higher than the cases (23.6 kg/m^2; SD, 4.1). Both groups were similar in relation to the hours spent in various forms of activity and in total METs expended per week.

Table 1 Background characteristics of cases and controls in the Singapore Lymphoma Study, 2004–2008

Categories	Controls (n = 830)		Cases (n = 541)		p value*
	No	%	No	%	
Age (years)					
Range	18–87		18–90		<0.001
Mean (SD)	50.3	16.0	54.2	16.0	
Gender					
Male	495	59.6	315	58.2	0.60
Female	335	40.4	226	41.8	
Ethnic group					
Chinese	551	66.4	417	77.1	<0.001
Malay	161	19.4	89	16.5	
Indian	118	14.2	35	6.5	
Education					
No education	77	9.3	59	11.0	0.09
≤6 years	237	28.6	139	25.9	
7–10 years	286	34.5	162	30.2	
>10 years	230	27.7	176	32.8	
Current housing type					
Public govt housing (≤3 rooms)	267	32.2	115	21.5	<0.001
Public govt housing (>3 rooms)	511	61.6	347	65.0	
Private condominium/ landed property	41	4.9	69	12.9	
Others (e.g., nursing home)	11	1.3	3	0.6	
Country of birth					
Singapore/Malaysia	786	94.7	482	89.9	0.001
Other Asian countries[a]	44	5.3	54	10.1	
History of cancer in the first-degree relatives					
Yes	178	21.7	177	34.4	<0.001
No	644	78.4	337	65.6	
Mean adult BMI (kg/m^2) (SD)	25.0	5.3	23.6	4.1	<0.001
Mean physical activity (in metabolic equivalent intensity level, MET/ week) in last year (SD)	264.6	51.7	260.9	52.7	0.21

SD standard deviation, *BMI* body mass index

* Variables were tested by chi-square test (categorical) or t test (continuous)

[a] Other Asian countries including China, Taiwan, Hong Kong, Indonesia, Philippines, India, Pakistan, and others

Table 2 shows the histological subtypes of lymphoid malignancies among cases recruited in the Singapore Lymphoma Study. There were 404 B-cell NHL (74.7 %), including 243 diffuse large B-cell lymphoma, 64 follicular lymphoma, 52 marginal zone B-cell lymphoma, 13 multiple myeloma, and 32 other B-cell types (e.g., CLL, SLL); 61 T-/NK-cell NHL (11.3 %), 74 HL (13.7 %), and 2 composite lymphomas (0.4 %). The distribution of subtypes was similar between genders.

The associations between pigmentary and sun sensitivity characteristics and malignant lymphoma are shown in Table 3. Limited variation was observed in eye and hair color since the majority of subjects were reported as having black/dark brown eyes (96.3 %) and black hair (97.0 %). Although the number of persons with natural lighter-colored hair (brown, as opposed to black) was small, this characteristic conferred a twofold risk of all lymphomas combined (OR, 1.95; 95 % CI, 0.98–3.89). Forty percent of the study populations have ever had sunburn in their lifetime; 20.4 % of controls and 16.9 % of cases experienced painful/severe burn after repeated sun exposure. There was no association between skin color and sun sensitivity (sunburn history, age at first sunburn or skin reaction to strong sunlight without protection) and risk of either NHL or HL.

The prevalence of using sun protection was very low in this study population, only 4.0 % of participants had ever used sun protection during childhood (3.6 % used in school days and 3.4 % in non-school days). The usage was slightly higher in adulthood (9.1 % ever users, 6.2 % on working days, and 7.6 % on non-working days).

Occupational sun exposure

On average, cases and controls spent 1.4 h/day (SD, 2.3) and 1.5 h/day (SD, 2.3), respectively, working outdoors. Participants who had ever engaged in outdoor occupations had a decreased risk of NHL overall (OR, 0.75; 95 % CI,

Table 2 Histological subtypes of lymphoid neoplasms in the Singapore Lymphoma Study, 2004–2008

Lymphoma subtype	Male		Female		Total	
	n	%	*n*	%	*n*	%
Hodgkin lymphoma (HL)	46	14.6	28	12.4	74	13.7
Non-Hodgkin lymphoma (NHL)	267	84.8	198	87.6	465	86.0
B-cell neoplasms	225	71.4	179	79.2	404	74.7
Diffuse large B-cell lymphoma and Burkitt lymphoma	132	41.9	111	49.1	243	44.9
Follicular lymphoma	39	12.4	25	11.1	64	11.8
Marginal zone B-cell lymphoma	28	8.9	24	10.6	52	9.6
Multiple myeloma	7	2.2	6	2.7	13	2.4
Other B-cell types[a]	19	6.0	13	5.8	32	5.9
T- cell and NK-cell neoplasms	42	13.3	19	8.4	61	11.3
Composite lymphoma (HL + NHL)	2	0.6	0	0	2	0.4
Total (% of total)	315	58.2	226	41.8	541	100

[a] Other B-cell types included chronic lymphocytic leukemia/small lymphocytic lymphoma; mantle cell lymphoma; immunoblastic lymphoma; or NHL NOS

Table 3 Association between pigmentary and sun sensitivity and risk of lymphoid malignancies in the Singapore Lymphoma Study, 2004–2008

Pigmentary and sun sensitivity characteristics	Controls		Lymphoid neoplasms				Non-Hodgkin lymphoma				Hodgkin lymphoma			
	n	%	*n*	%	OR[a]	(95 % CI)	*n*	%	OR[a]	(95 % CI)	*n*	%	OR[a]	(95 % CI)
Hair color (natural)														
Black	810	97.7	511	95.9	1.00	(ref)	441	96.3	1.00	(ref)	68	93.2	1.00	(ref)
Brown (dark/light)	19	2.3	22	4.1	1.95	(0.98–3.89)	17	3.7	1.98	(0.93–4.19)	5	6.9	2.16	(0.67–6.94)
Eye color														
Black/dark brown	799	96.4	512	96.2	1.00	(ref)	439	96.1	1.00	(ref)	71	97.3	1.00	(ref)
Light brown	30	3.6	20	3.8	1.38	(0.68–2.78)	18	3.9	1.42	(0.67–3.00)	2	2.7	1.37	(0.30–6.24)
Skin color														
White/light tan	350	42.2	263	49.4	1.00	(ref)	240	52.5	1.00	(ref)	23	31.5	1.00	(ref)
Tan	383	46.2	241	45.3	0.90	(0.69–1.19)	196	42.9	0.79	(0.59–1.06)	43	58.9	1.59	(0.89–2.86)
Dark brown/black	96	11.6	28	5.3	0.65	(0.34–1.21)	21	4.6	0.67	(0.33–1.36)	7	9.6	0.57	(0.17–1.97)
History of sunburn														
Never	490	59.1	318	59.8	1.00	(ref)	281	61.5	1.00	(ref)	35	48.0	1.00	(ref)
Ever	339	40.9	214	40.2	0.97	(0.74–1.28)	176	38.5	0.98	(0.73–1.32)	38	52.1	1.00	(0.56–1.77)
Skin reaction to strong sunlight with no protection														
Go brown only	614	74.2	416	78.2	1.00	(ref)	365	79.9	1.00	(ref)	49	67.1	1.00	(ref)
Mildly burnt and tanned	45	5.4	26	4.9	0.82	(0.47–1.43)	22	4.8	0.90	(0.49–1.63)	41	5.5	0.62	(0.20–1.87)
Painful burn and peeling	158	19.1	83	15.6	0.76	(0.54–1.06)	64	14.0	0.70	(0.49–1.01)	9	26.0	1.05	(0.57–1.93)
Severely burnt and blistering	11	1.3	7	1.3	0.65	(0.20–2.16)	6	1.3	0.56	(0.15–2.13)	1	1.4	1.28	(0.15–10.8)

Numbers did not add up to 830 controls and 541 cases due to missing data

ref referent, *OR* odds ratio, *CI* confidence intervals

[a] OR, odds ratio adjusted for age (continuous), gender (male/female), ethnic (Chinese/Malay/Indian), education (never/≤6/7–10/>10 years), housing type (public housing ≤3 rooms/public housing >3 rooms/private housing/others), BMI (continuous), and history of any cancer in the first-degree relatives (yes/no) in multiple logistic regression model

0.55–1.03) and for B-cell NHL subtypes (OR, 0.73; 95 % CI, 0.53–1.02) compared with those who only worked indoors (Table 4). Further adjustment of hair color, skin sensitivity, height, weight, and energy expenditure on physical activities did not change the risk estimates materially and were not included in the final models.

Recreational sun exposure

During childhood, cases and controls spent, on average, 11.9 h/week (SD, 15.4) and 13.1 h/week (SD, 14.6), respectively, on recreational activities under the sun. The amount of time was reduced substantially to 3.2 h/week (SD, 6.9) and 4.0 h/week (SD, 7.6), respectively, during adulthood. For all types of activities, women participants spent less time in the sun than men. The weekly exposure in adulthood was 4.8 h (SD, 8.2) in men and 2.8 (SD, 6.3) in women; corresponding figures for childhood exposure are 15.6 h (SD, 15.1) for boys and 9.4 h (SD, 13.0) for girls.

Compared to those without regular recreational sun exposure, those who regularly spent at least 30 min/day outdoors on non-school days during childhood had a 38 % reduction in risk of lymphoma. A significant association was observed for NHL (OR, 0.62; 95 % CI, 0.46–0.83), and for B-cell lymphoma (OR, 0.56; 95 % CI, 0.41–0.77) in particular. Similarly, the risk of NHL among those who reported regular recreational sun exposure in adulthood on non-working days was also significantly reduced (OR, 0.70; 95 % CI, 0.51–0.97). For T-cell lymphoma, the observed reduction (OR, 0.19; 95 % CI, 0.06–0.54) was based on a small number of cases.

In terms of weekly recreational sun exposure, a significant risk reduction was observed consistently for lymphoid neoplasms (OR, 0.73; 95 % CI, 0.55–0.96), NHL (OR, 0.73; 95 % CI, 0.54–0.99), and B-cell NHL (OR, 0.69; 95 % CI, 0.51–0.95) in childhood, but not in adulthood.

Gender differences

The protective effect of childhood sun exposure was more evident in women (Table 5). There was a 50–60 % risk reduction observed in women on school days (OR, 0.54; 95 % CI, 0.34–0.87), non-school days (OR, 0.38; 95 % CI, 0.23–0.61), and on combined weekly exposure (OR, 0.43; 95 % CI, 0.27–0.68).

Discussion

To our knowledge, this is the first epidemiologic study of sun exposure and risk of malignant lymphomas conducted both in an Asian population and in a tropical location. Our results suggest that in this study population, regular, leisure-time sun exposure in both childhood and adulthood is associated with a reduced risk of non-Hodgkin lymphoma. When stratified by gender, the reduction in risk conferred by regular childhood sun exposure was stronger in women than in men.

Recreational sun exposure

Our findings on the protective association of recreational sun exposure are generally consistent with other studies on personal sun exposure in the West [22, 23, 27, 28, 30–32]. A case–control study by Hughes et al. in Australia was the first to report an inverse association between personal ultraviolet radiation exposure and the risk of NHL. There were reduced risks with exposure on non-working days in adulthood, suggesting that an intermittent pattern of sun exposure might be protective; and the protective effect of year-round sun exposure was the greatest during childhood [26]. The InterLymph analysis of 10 case–control studies in the West, consisting of 8,243 cases and 9,697 controls, reported a pooled odds ratio of 0.76 (95 % CI, 0.63–0.91) for recreational sun exposure [23]. A recent case–control study in Rochester [32] reported a decrease in NHL risk in subjects who had sunbathed more than once per week versus never (OR, 0.28; 95 % CI, 0.10–0.79) over the past 10 years. A Scandinavian study also demonstrated a reduced risk in NHL, especially the B-cell type, with increasing adult personal sun exposure, and among subjects who had spent vacations in sunny southern climates [30]. In contrast, a population-based case–control study of Connecticut women showed an increased risk of NHL among those who reported spending time (between 9 am and 3 pm) in strong sun during summer (OR, 1.7; 95 % CI, 1.2–2.4) [25].

The reason for a strong association in women is not immediately clear. It is possible that the effect is greater because of the lower baseline exposure in this group, compared with their male counterparts. Our results were supported by the Australian study reported by Hughes [26] that the association of sun exposure and the NHL risk reduction was apparently stronger in women. In our population, the higher exposure hours in childhood than adulthood may be the reason for the apparently stronger association in childhood, as suggested by the Australian study.

Occupational sun exposure

The average occupational sun exposure reported in our study was comparable with another study on pterygia and sun exposure in Singapore in 1998 and 2000 [33, 34]. The control group of 125 subjects was spending on average 1.6 h per day (SD, 1.6) currently and 1.9 h per day (SD, 1.8) at 5 years ago [33]. We detected a marginal protective effect of occupational exposure in adults, although this was not evident in the pooled analysis based on the InterLymph data [23]. However, Epilymph reported a similar result, which was only limited to the Diffuse large B-cell lymphoma subtype (OR, 0.72; 95 % CI, 0.54–0.97) [28]. Most

Table 4 Association between outdoor sun exposure for recreational or occupational purposes and risk of lymphoid malignancies in the Singapore Lymphoma Study, 2004–2008

Outdoor sun exposure	Ctrl	Lymphoid neoplasms			Non-Hodgkin lymphoma									Hodgkin lymphoma		
					NHL			B-cell NHL			T-cell NHL					
	n	*n*	OR[a]	(95 % CI)	*n*	OR[a]	(95 % CI)	*n*	OR[a]	(95 % CI)	*n*	OR[a]	(95 % CI)	*n*	OR[a]	(95 % CI)
Occupational																
Indoor work only	372	262	1.00	(ref)	233	1.00	(ref)	207	1.00	(ref)	26	1.00	(ref)	29	1.00	(ref)
Mixed indoor ± outdoor work	373	220	0.76	(0.56–1.02)	192	0.75	(0.55–1.03)	162	0.73	(0.53–1.02)	28	1.10	(0.55–2.21)	27	0.76	(0.39–1.47)
Regular recreational																
Daily																
Childhood on school days																
No regular exposure	387	268	1.00	(ref)	240	1.00	(ref)	215	1.00	(ref)	25	1.00	(ref)	27	1.00	(ref)
>30 min exposure/day	434	246	0.78	(0.59–1.04)	200	0.80	(0.60–1.09)	169	0.76	(0.56–1.04)	32	1.46	(0.74–2.90)	45	0.80	(0.45–1.43)
Childhood on non-school days																
No regular exposure	385	295	1.00	(ref)	261	1.00	(ref)	236	1.00	(ref)	25	1.00	(ref)	33	1.00	(ref)
>30 min exposure/day	436	219	0.62	(0.47–0.81)**	179	0.62	(0.46–0.83)**	148	0.56	(0.41–0.77)**	31	1.35	(0.70–2.60)	39	0.69	(0.40–1.22)
Adult on non-working days																
No regular exposure	563	394	1.00	(ref)	353	1.00	(ref)	302	1.00	(ref)	51	1.00	(ref)	40	1.00	(ref)
>30 min exposure/day	241	116	0.76	(0.57–1.02)	95	0.70	(0.51–0.97)*	90	0.83	(0.60–1.16)	5	0.19	(0.06–0.54)**	21	1.03	(0.57–1.87)
Weekly[b]																
Childhood per week																
No regular exposure	329	241	1.00	(ref)	217	1.00	(ref)	195	1.00	(ref)	22	1.00	(ref)	23	1.00	(ref)
>1 h exposure/week	492	273	0.73	(0.55–0.96)**	223	0.73	(0.54–0.99)*	189	0.69	(0.51–0.95)*	34	1.27	(0.64–2.53)	49	0.80	(0.44–1.46)
Adult per week																
No regular exposure	543	369	1.00	(ref)	331	1.00	(ref)	286	1.00	(ref)	45	1.00	(ref)	37	1.00	(ref)
>1 h exposure/week	261	141	0.92	(0.69–1.21)	117	0.87	(0.64–1.17)	106	0.96	(0.70–1.31)	11	0.49	(0.23–1.04)	24	1.13	(0.63–2.03)

Numbers did not add up to 830 controls and 541 cases due to missing data

Ctrl control, *n* number, *ref* reference group, *CI* confidence intervals, * *p* value <0.05; ** *p* value <0.01

[a] OR, Odds ratio adjusted for age (continuous), gender (male/female), ethnicity (Chinese/Malay/Indian), skin color (white-light tan/tan/dark brown-black), education (never/≤6/7–10/>10 years), housing type (public housing ≤3 rooms/public housing >3 rooms/private housing/others), BMI (continuous), and history of any cancer in the first-degree relatives (yes/no) in multiple logistic regression model. (Further adjustment of hair color, skin sensitivity, height, weight, physical activity (in METs) did not materially affect risk estimates.)

[b] Weekly sun exposure = 5 × school days + 2 × non-school days (age <20 years); or 5 × working days + 2 × non-working days (age ≥20 years)

Table 5 The association between childhood sun exposure and non-Hodgkin lymphoma by gender

Recreational sun exposure in childhood	Males			Females			p interaction
	Nco/Nca	OR[a]	(95 % CI)	Nco/Nca	OR[a]	(95 % CI)	
Daily							
On school days							
No regular exposure	193/104	1.00	(ref)	194/136	1.00	(ref)	0.03
>30 min exposure/day	300/147	1.03	(0.71–1.49)	134/53	0.54	(0.34–0.87)**	
On non-school days							
No regular exposure	182/111	1.00	(ref)	203/150	1.00	(ref)	0.01
>30 min exposure/day	311/140	0.82	(0.57–1.17)	125/39	0.38	(0.23–0.61)***	
Weekly[b]							
No regular exposure	153/84	1.00	(ref)	176/133	1.00	(ref)	0.01
>1 h exposure/week	340/167	0.97	(0.70–1.45)	152/56	0.43	(0.27–0.68)***	

Numbers did not add up to 830 controls and 541 cases due to missing data

Nco no of controls, *Nca* no of NHL cases, *ref* referent, *OR* odds ratio, *CI* confidence intervals, ** p value <0.01; *** p value <0.001

[a] OR, odds ratio adjusted for age (continuous), ethnic (Chinese/Malay/Indian), skin color (white-light tan/tan/dark brown-black), education (never/<6/7–10/>10 years), housing type (public housing ≤3 rooms/public housing >3 rooms/private housing/others), BMI (continuous), and history of any cancer in the first-degree relatives (yes/no) in multiple logistic regression model

[b] Weekly sun exposure = 5 × school days + 2 × non-school days (age <20 years)

of the studies in the West did not detect any association between occupational sun exposure and NHL risk.

One possible explanation for the difference in the associations observed for recreational and occupational sun exposure is that the intermittent pattern of the former plays a key role [23, 26]. It has also been proposed that long periods of exposure do not result in a corresponding increase in the active compound due to a ceiling effect [35].

Possible mechanisms of protection

It is known that ultraviolet radiation can function as a carcinogen and has immunosuppressive functions [36] and that skin aging and sunburn are mainly caused by DNA-damaging UVA (95 % of UV radiation). The proposed mechanism by which sun exposure may reduce risk of lymphoid neoplasms is by means of vitamin D-related pathways [37]. The main source of vitamin D (cholecalciferol) production in humans is the skin, where it is synthesized from 7-dehydrocholesterol following exposure to UV-B radiation in sunlight [35]. Experimental studies have demonstrated that the active form of vitamin D has anti-proliferative and pro-differentiation effects on tumor cells [38] and lymphoma cell lines [39]. Data on vitamin D levels in Asian populations such as Singapore suggest that vitamin D insufficiency may be prevalent among older individuals [40–42]; to date, epidemiologic studies that have examined the association between self-reported dietary vitamin D intake and NHL have all been conducted in Western populations and have yielded null associations [22, 31].

Strength and limitations

The primary aim of this study was to evaluate whether the previously described effects of sun exposure on the risk of lymphoid neoplasms can be replicated in an Asian population living in the topics. Its strengths are that data were collected using standardized techniques, with effort made to maintain comparability with previous questionnaires used in other populations. The multi-center design provided us access to a representative sample of eligible incident cases in this country.

At the same time, we are mindful of the limitations that are inherent in the retrospective nature of this study, and the limited sample size. Specifically, we were unable to make inferences about the effect of sun exposure on Hodgkin lymphoma, and on the T-cell NHL subtypes, although the risk estimates suggested interesting differences. The relatively low participation rate (62.4 %) in our hospital controls may introduce a selection bias, but it is unlikely that this is related to sun exposure in a way that would account for the associations observed. Hospital controls may be considered more likely to be ill than the general population, and this would result in less, rather than more, time spent outdoors in the sun, and hence any bias would act conservatively. Further, in order to reduce the effect of potential bias due to medical conditions that are associated with higher sun exposure, not more than 10 % of our controls had a similar admission diagnosis. We also acknowledge that reporting and recall bias could occur in this study, but as the hypothesis regarding sun exposure and lymphoma risk is not widely known in the general

population, we would expect such a misclassification to be non-differential.

As sun exposure (and not vitamin D) was the primary exposure studied, we did not include dietary sources of vitamin D. This was due to the relatively low intake of vitamin D-rich food sources in this population, and difficulties in obtaining accurate data on supplement intake, and we recognize that this limits the extent to which we can attribute our findings to a particular biologic mechanism.

Conclusion

In conclusion, we find that in this Asian population, intermittent recreational sun exposure in childhood and adulthood is inversely associated with the risk of developing non-Hodgkin lymphoma. These findings, which are consistent with the growing evidence across various populations, should be replicated in larger studies in other similar contexts. The underlying mechanism, including a possible role for vitamin D in immune modulation and lymphomagenesis, deserves further study.

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Conflict of interest None.

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